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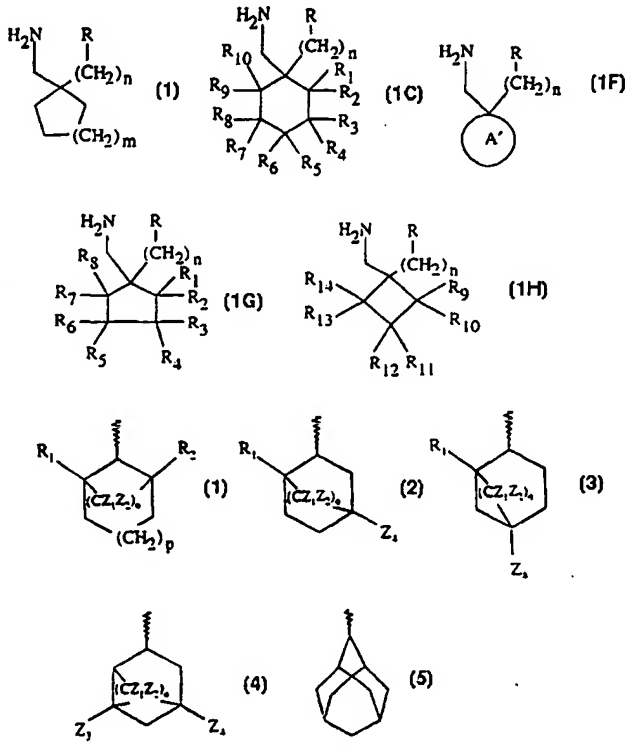
(54) Title: 1-SUBSTITUTED-1-AMINOMETHYL-CYCLOALKANE DERIVATIVES (=GABAPENTIN ANALOGUES), THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS

(57) Abstract

Novel amines of formulas (1), (1C), (1F), (1G) and (1H) or a pharmaceutical acceptable salt thereof wherein n is an integer of from 0 to 2; m is an integer of from 0 to 3; R is sulfonamide, amide, phosphonic acid, heterocycle, sulfonic acid, or hydroxamic acid; A' is a bridged ring selected from (1), (2), (3), (4), (5) wherein is the point of attachment; Z_1 to Z_4 are each independently selected from hydrogen and methyl; o is an integer of from 1 to 4; and p is an integer of from 0 to 2. In formula (1) above R cannot be sulfonic acid when m is 2 and n is 1 are disclosed and are useful as agents in the treatment of epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological disorders, inflammatory diseases, and gastrointestinal disorders, especially irritable bowel syndrome.



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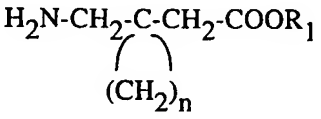
1-SUBSTITUTED-1-AMINOMETHYL-CYCLOALKANE DERIVATIVES (=GABAPENTIN ANALOGUES), THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISORDERS

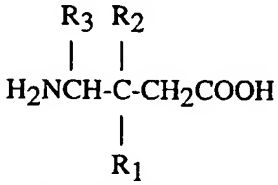
BACKGROUND OF THE INVENTION

Compounds of formula



wherein R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in United States Patent Number 4,024,175 and its divisional United States Patent Number 4,087,544. The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

Compounds of formula



wherein R_1 is a straight or branched alkyl group having from 1 to 6 carbon atoms, phenyl, or cycloalkyl having from 3 to 6 carbon atoms; R_2 is hydrogen or methyl; and R_3 is hydrogen, methyl, or carboxyl are known in United States Patent Number 5,563,175 and various divisionals. These patents are hereby incorporated by reference.

SUMMARY OF THE INVENTION

The compounds of the instant invention are novel amines and their pharmaceutically acceptable salts useful in a variety of disorders. The disorders include: epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, neuropathological

disorders, inflammatory diseases, and gastrointestinal disorders, especially irritable bowel syndrome.

The compounds of the invention are those of formulas 1, 1C, 1F, 1G, and 1H below.

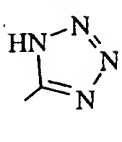
Preferred compounds are those wherein R is a sulfonamide selected from $-NHSO_2R^{15}$ or $-SO_2NHR^{15}$ wherein R^{15} is straight or branched alkyl or trifluoromethyl.

Especially preferred is N-[2-(1-aminomethyl-cyclohexyl)-ethyl]-methanesulfonamide.

Other preferred compounds are those wherein R is a phosphonic acid, $-PO_3H_2$.

Especially preferred are (1-aminomethyl-cyclohexylmethyl)-phosphonic acid and (2-aminomethyl-4-methyl-pentyl)-phosphonic acid.

Other preferred compounds are those wherein R is a heterocycle selected from: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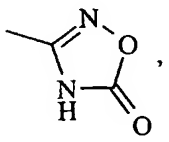
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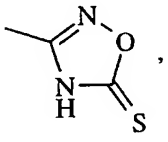
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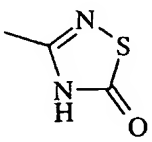
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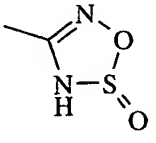
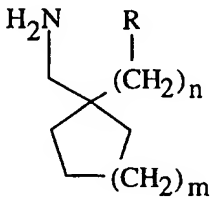

.

Especially preferred are C-[1-(1H-tetrazol-5-ylmethyl)cyclohexyl]-methylamine and 4-methyl-2-(1H-tetrazol-5-ylmethyl)-pentylamine.

DETAILED DESCRIPTION OF THE INVENTION

The amines of the instant invention are compounds of formulas 1, 1C, 1F, 1G, and 1H and the pharmaceutically acceptable salts thereof.

The compounds of the invention are those of formula



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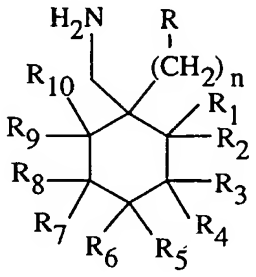

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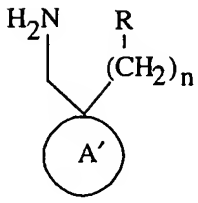

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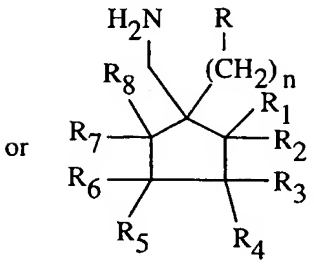

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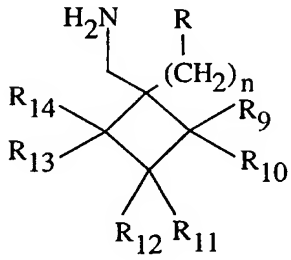


or

IG IH

or a pharmaceutically acceptable salt thereof wherein:

n is an integer of from 0 to 2;

m is an integer of from 0 to 3;

R is sulfonamide,

amide,

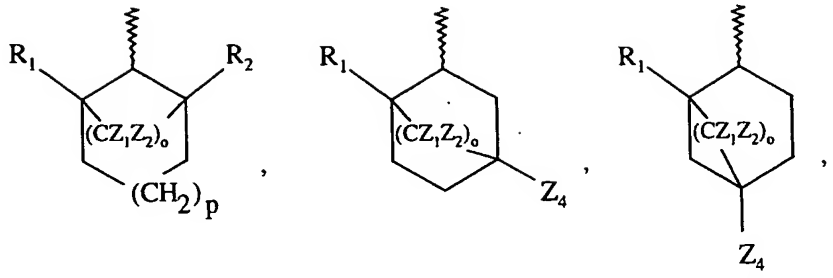
phosphonic acid,

heterocycle,

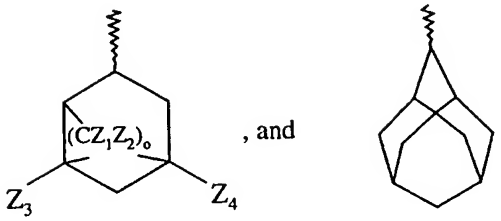
sulfonic acid, or

hydroxamic acid;

A′ is a bridged ring selected from



(1) (2) (3)



(4) (5)

wherein

≋ is the point of attachment;

Z_1 to Z_4 are each independently selected from hydrogen and methyl;

o is an integer of from 1 to 4; and

p is an integer of from 0 to 2.

In Formula 1 above R cannot be sulfonic acid when m is 2 and n is 1. (Suman-Chaulan N., et al., European Journal of Pharmacology, 1993;244:293-301.)

Preferred compounds of the invention are:

(1-Aminomethyl-cyclohexylmethyl)-phosphonic acid;

(1R-trans)(1-Aminomethyl-3-methyl-cyclohexylmethyl)-phosphonic acid;

(trans)(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-phosphonic acid;

(1R-trans)(1-Aminomethyl-3-methyl-cyclopentylmethyl)-phosphonic acid;

(1S-cis)(1-Aminomethyl-3-methyl-cyclopentylmethyl)-phosphonic acid;

(1S-trans)(1-Aminomethyl-3-methyl-cyclopentylmethyl)-phosphonic acid;

(1R-cis)(1-Aminomethyl-3-methyl-cyclopentylmethyl)-phosphonic acid;

(1α,3α,4α)(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-phosphonic acid;

(1α,3β,4β)(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-phosphonic acid;

(R)(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-phosphonic acid;

(S)(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-phosphonic acid;

(1-Aminomethyl-3,3-dimethyl-cyclobutylmethyl)-phosphonic acid;

2-(1-Aminomethyl-cyclohexyl)-N-hydroxy-acetamide;

(1S-trans)2-(1-Aminomethyl-3-methyl-cyclohexyl)-N-hydroxy-acetamide;

(trans)2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

(1S-cis)2-(1-Aminomethyl-3-methyl-cyclopentyl)-N-hydroxy-acetamide;

(1R-trans)2-(1-Aminomethyl-3-methyl-cyclopentyl)-N-hydroxy-acetamide;

(1R-cis)2-(1-Aminomethyl-3-methyl-cyclopentyl)-N-hydroxy-acetamide;

(1S-trans)2-(1-Aminomethyl-3-methyl-cyclopentyl)-N-hydroxy-acetamide;

(1α,3α,4α)2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

(1α,3β,4β)2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

(S)2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

(R)2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

2-(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-N-hydroxy-acetamide;

N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclohexyl)-ethyl]-methanesulfonamide;

(trans)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1R-trans)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1R-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1α,3α,4α)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1α,3β,4β)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

(S)N-[2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

(R)N-[2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

N-[2-(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-ethyl]-methanesulfonamide;

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(trans)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1R-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1R-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1S-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1α,3α,4α)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1α,3β,4β)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(S)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(R)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(1-Aminomethyl-3,3-dimethyl-cyclobutylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(trans)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1R-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1R-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1S-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1α,3α,4α)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1α,3β,4β)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(S)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(R)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

3-(1-Aminomethyl-3,3-dimethyl-cyclobutylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[1-(1H-Tetrazol-5-ylmethyl)-cyclohexyl]-methylamine;

(1S-cis)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclohexyl]-methylamine;

(trans)C-[3,4-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1S-cis)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1R-trans)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1R-cis)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1S-trans)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1α,3α,4α)C-[3,4-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1α,3β,4β)C-[3,4-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(S)C-[3,3-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(R)C-[3,3-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

C-[3,3-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclobutyl]-methylamine;

N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclohexyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(trans)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1R-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1S-trans)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1R-trans)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1α,3α,4α)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1α,3β,4β)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(S)N-[2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(R)N-[2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

N-[2-(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclohexylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(trans)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1R-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1S-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1R-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1α,3α,4α)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1α,3β,4β)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(S)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(R)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

3-(1-Aminomethyl-3,3-dimethyl-cyclobutylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[1-(2-Oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclohexyl]-methylamine;

(1S-cis)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclohexyl]-methylamine;

(trans)C-[3,4-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1S-cis)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1R-trans)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1R-cis)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1S-trans)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1α,3α,4α)C-[3,4-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1α,3β,4β)C-[3,4-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(S)C-[3,3-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(R)C-[3,3-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

C-[3,3-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclobutyl]-methylamine;

(1-Aminomethyl-cyclohexyl)-methanesulfonamide;

(1R-trans)(1-Aminomethyl-3-methyl-cyclohexyl)-methanesulfonamide;

(trans)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonamide;

(1S-trans)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonamide;

(1R-cis)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonamide;

(1R-trans)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonamide;

(1S-cis)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonamide;

(1α,3β,4β)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonamide;

(1α,3α,4α)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonamide;

(R)(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-methanesulfonamide;

(S)(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-methanesulfonamide;

(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-methanesulfonamide;

(1-Aminomethyl-cyclohexyl)-methanesulfonic acid;

(1R-trans) (1-Aminomethyl-3-methyl-cyclohexyl)-methanesulfonic acid;

(trans)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonic acid;

(1S-trans)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonic acid;

(1S-cis)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonic acid;

(1R-trans)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonic acid;

(1R-cis)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonic acid;

(1α,3β,4β)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonic acid;

(1α,3α,4α)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonic acid;

(R)(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-methanesulfonic acid;

(S)(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-methanesulfonic acid;

(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-methanesulfonic acid;

(1-Aminomethyl-cyclopentylmethyl)-phosphonic acid;

2-(1-Aminomethyl-cyclopentyl)-N-hydroxy-acetamide;

N-[2-(1-Aminomethyl-cyclopentyl)-ethyl]-methanesulfonamide;

3-(1-Aminomethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(1-Aminomethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[1-(1H-Tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

N-[2-(1-Aminomethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

3-(1-Aminomethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[1-(2-Oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1-Aminomethyl-cyclopentyl)-methanesulfonamide;

(1-Aminomethyl-cyclopentyl)-methanesulfonic acid;

(9-Aminomethyl-bicyclo[3.3.1]non-9-ylmethyl)-phosphonic acid;

2-(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-N-hydroxy-acetamide;

N-[2-(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-ethyl]-methanesulfonamide;

3-(9-Aminomethyl-bicyclo[3.3.1]non-9-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(9-Aminomethyl-bicyclo[3.3.1]non-9-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[9-(1H-Tetrazol-5-ylmethyl)-bicyclo[3.3.1]non-9-yl]-methylamine;

N-[2-(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

3-(9-Aminomethyl-bicyclo[3.3.1]non-9-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[9-(2-Oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-bicyclo[3.3.1]non-9-yl]-methylamine;

(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-methanesulfonamide;

(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-methanesulfonic acid;

(2-Aminomethyl-adamantan-2-ylmethyl)-phosphonic acid;

2-(2-Aminomethyl-adamantan-2-yl)-N-hydroxy-acetamide;

N-[2-(2-Aminomethyl-adamantan-2-yl)-ethyl]-methanesulfonamide;

3-(2-Aminomethyl-adamantan-2-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(2-Aminomethyl-adamantan-2-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[2-(1H-Tetrazol-5-ylmethyl)-adamantan-2-yl]-methylamine;

N-[2-(2-Aminomethyl-adamantan-2-yl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

3-(2-Aminomethyl-adamantan-2-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[2-(2-Oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-adamantan-2-yl]-methylamine;

(2-Aminomethyl-adamantan-2-yl)-methanesulfonamide;

(2-Aminomethyl-adamantan-2-yl)-methanesulfonic acid;

(1-Aminomethyl-cycloheptylmethyl)-phosphonic acid;

2-(1-Aminomethyl-cycloheptyl)-N-hydroxy-acetamide;

N-[2-(1-Aminomethyl-cycloheptyl)-ethyl]-methanesulfonamide;

3-(1-Aminomethyl-cycloheptylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(1-Aminomethyl-cycloheptylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[1-(1H-Tetrazol-5-ylmethyl)-cycloheptyl]-methylamine;

N-[2-(1-Aminomethyl-cycloheptyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

C-[1-(2-Oxo-2,3-dihydro-2 l4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cycloheptyl]-methylamine;

(1-Aminomethyl-cycloheptyl)-methanesulfonamide; and

(1-Aminomethyl-cycloheptyl)-methanesulfonic acid.

Since amino acids are amphoteric, pharmacologically compatible salts can be salts of appropriate inorganic or organic acids, for example, hydrochloric, sulphuric, phosphoric, acetic, oxalic, lactic, citric, malic, salicylic, malonic, maleic, succinic, methanesulfonic acid, and ascorbic. Starting from corresponding hydroxides or carbonates, salts with alkali metals or alkaline earth metals, for example, sodium, potassium, magnesium, or calcium are formed. Salts with quaternary ammonium ions can also be prepared with, for example, the tetramethyl-ammonium ion. The carboxyl group of the amino acids can be esterified by known means.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Novel intermediates useful in the preparation of the final compounds are included in the invention.

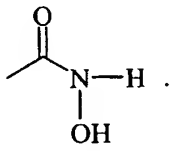
The terms used to define the invention are as described below.

Sulfonamides are those of formula $-NHSO_2R^{15}$ or $-SO_2NHR^{15}$ wherein R^{15} is a straight or branched alkyl group of from 1 to 6 carbons or a trifluoromethyl.

Amides are compounds of formula $-NHCOR^{12}$ wherein R^{12} is straight or branched alkyl of from 1 to 6 carbons, benzyl, and phenyl.

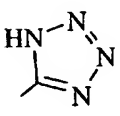
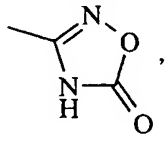
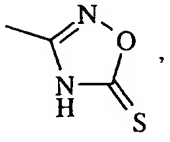
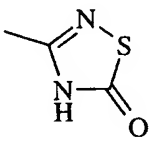
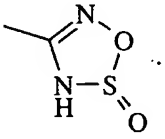
Phosphonic acids are $-PO_3H_2$.

Sulfonic acids are $-SO_3H$.

Hydroxamic acid is  .

Heterocycles are groups of from 1 to 2 rings, with from 1 to 6 heteroatoms selected from oxygen, nitrogen, and sulfur.

Preferred heterocycles are

 ,  ,  ,  , and  .

The term alkyl is a straight or branched group of from 1 to 11 carbon atoms including but not limited to methyl, ethyl, propyl, n-propyl, isopropyl, butyl, 2-butyl, tert-butyl, pentyl, hexyl, and n-hexyl, heptyl, octyl, nonyl, decyl, and undecyl except as where otherwise stated.

The cycloalkyl groups are from 3 to 8 carbons and are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl unless otherwise stated.

The benzyl and phenyl groups may be unsubstituted or substituted by from 1 to 3 substituents selected from hydroxy, carboxy, carboalkoxy, halogen, CF_3, nitro, alkyl, and alkoxy. Preferred are halogens.

Alkoxy is as defined above for alkyl.

Halogen is fluorine, chlorine, and bromine and preferred are fluorine and chlorine.

Carboalkoxy is -COOalkyl wherein alkyl is as described above. Preferred are carbomethoxy and carboethoxy.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

The radioligand binding assay using [^{3}H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue was used ("The Novel Anti-convulsant Drug, Gabapentin, Binds to the $\alpha_2\delta$ Subunit of a Calcium Channel", Gee N.S., et al., J. Biol. Chem., 1996;271(10):5768-5776).

The compounds of the invention show good binding affinity to the $\alpha_2\delta$ subunit. Gabapentin (Neurontin®) is about 0.10 to 0.12 μM in this assay. Since the compounds of the instant invention also bind to the subunit, they are expected to exhibit pharmacologic properties comparable to gabapentin. For example, as agents for convulsions, anxiety, and pain.

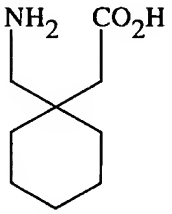
TABLE 1

Example	α2δ Assay	Pain Model % MPE			
	IC_{50} (nM)	1 Hour	2 Hours	1 Hour	2 Hours
C-[1-(1H-Tetrazol-5-ylmethyl)-cyclohexyl]-methylamine; hydrochloride	0.203	na	na	60	100
3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one; hydrochloride	0.17	80.6	76.1	20	40
C-[9-(1H-Tetrazol-5-ylmethyl)-2-adamantyl]-methylamine; hydrochloride	4.37				
C-[9-(1H-Tetrazol-5-ylmethyl)-bicyclo[3.3.1]non-9-yl]-methylamine; hydrochloride	3.7				
3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-thione; hydrochloride	4.22			0	0
Trans C-[1-(1H-Tetrazol-5-ylmethyl)-3,4-dimethylcyclopentyl]-methylamine; hydrochloride	0.108				
N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-methanesulfonamide	>10	0.3	-0.9		0
N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-t-butylamide	>10	1.6	-4.8		0
N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-malonamic acid	>10				
N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-3-phenyl-propionamide; hydrochloride	>10				
N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-2-phenyl-acetamide; hydrochloride	>10				
Gabapentin	0.14	49.9	19.9	100	100

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one; hydrochloride was active in the carrageenan induced hyperalgesia assay. When dosed at 30 mg/kg orally in the rat, the compound increased paw withdrawal latency by 80.6% at 1 hour and 76% at 2 hours. By comparison, gabapentin at this dose caused a 49.9% increase at 1 hour and only a 19.9% increase at 2 hours. Thus, the former compound appears to have an antihyperalgesic effect of longer duration than gabapentin.

C-[1-(1H-Tetrazol-5-ylmethyl)-cyclohexyl]-methylamine hydrochloride, when tested in the DBA2 audiogenic seizure model at 10 mg/kg after oral dosing, gave 60% protection after 1 hour postdose, 100% protection after 2 hours postdose, 100% protection after 4 hours postdose, and 80% after 6 hours postdose. In the same assay, gabapentin, dosed at 10 mg/kg orally, gave no significant response. At 30 mg/kg it gave 100% protection at 2 hours postdose.

The compounds of the invention are related to Neurontin®, a marketed drug effective in the treatment of epilepsy. Neurontin® is 1-(aminomethyl)-cyclohexaneacetic acid of structural formula



The compounds of the invention are also expected to be useful in the treatment of epilepsy.

The present invention also relates to therapeutic use of the compounds of the mimetic as agents for neurodegenerative disorders.

Such neurodegenerative disorders are, for example, Alzheimer's disease, Huntington's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, and epilepsy.

The present invention also covers treating neurodegenerative disorders termed acute brain injury. These include but are not limited to: stroke, head trauma, and asphyxia.

Stroke refers to a cerebral vascular disease and may also be referred to as a cerebral vascular incident (CVA) and includes acute thromboembolic stroke.

Stroke includes both focal and global ischemia. Also, included are transient cerebral ischemic attacks and other cerebral vascular problems accompanied by cerebral ischemia such as in a patient undergoing carotid endarterectomy specifically or other cerebrovascular or vascular surgical procedures in general, or diagnostic vascular procedures including cerebral angiography and the like.

Pain refers to acute as well as chronic pain.

Acute pain is usually short-lived and is associated with hyperactivity of the sympathetic nervous system. Examples are postoperative pain and allodynia.

Chronic pain is usually defined as pain persisting from 3 to 6 months and includes somatogenic pains and psychogenic pains. Other pain is nociceptive.

Still other pain is caused by injury or infection of peripheral sensory nerves. It includes, but is not limited to pain from peripheral nerve trauma, herpes virus infection, diabetes mellitus, causalgia, plexus avulsion, neuroma, limb amputation, and vasculitis. Neuropathic pain is also caused by nerve damage from chronic alcoholism, human immunodeficiency virus infection, hypothyroidism, uremia, or vitamin deficiencies. Neuropathic pain includes, but is not limited to pain caused by nerve injury such as, for example, the pain diabetics suffer from.

Psychogenic pain is that which occurs without an organic origin such as low back pain, atypical facial pain, and chronic headache.

Other types of pain are: inflammatory pain, osteoarthritic pain, trigeminal neuralgia, cancer pain, diabetic neuropathy, restless leg syndrome, acute herpetic and postherpetic neuralgia, causalgia, brachial plexus avulsion, occipital neuralgia, gout, phantom limb, burn, and other forms of neuralgia, neuropathic and idiopathic pain syndrome.

Other incidents are head trauma, spinal cord trauma, or injury from general anoxia, hypoxia, hypoglycemia, and hypotension as well as similar injuries seen during procedures from embole, hyperfusion, and hypoxia.

The compounds of the instant invention will be useful in gastrointestinal disorders, for example, irritable bowel syndrome (IBS).

The instant invention would be useful in a range of incidents, for example, during cardiac bypass surgery, in incidents of intracranial hemorrhage, in perinatal asphyxia, in cardiac arrest, and status epilepticus.

A skilled physician will be able to determine the appropriate situation in which subjects are susceptible to or at risk of, for example, stroke as well as suffering from stroke for administration by methods of the present invention.

The compounds of the invention are also expected to be useful in the treatment of depression. Depression can be the result of organic disease, secondary to stress associated with personal loss, or idiopathic in origin. There is a strong tendency for familial occurrence of some forms of depression suggesting a mechanistic cause for at least some forms of depression. The diagnosis of depression is made primarily by quantification of alterations in patients' mood. These evaluations of mood are generally performed by a physician or quantified by a neuropsychologist using validated rating scales, such as the Hamilton Depression Rating Scale or the Brief Psychiatric Rating Scale. Numerous other scales have been developed to quantify and measure the degree of mood alterations in patients with depression, such as insomnia, difficulty with concentration, lack of energy, feelings of worthlessness, and guilt. The standards for diagnosis of depression as well as all psychiatric diagnoses are collected in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) referred to as the DSM-IV-R manual published by the American Psychiatric Association, 1994.

GABA is an inhibitory neurotransmitter with the central nervous system. Within the general context of inhibition, it seems likely that GABA-mimetics might decrease or inhibit cerebral function and might therefore slow function and decrease mood leading to depression.

The compounds of the instant invention may produce an anticonvulsant effect through the increase of newly created GABA at the synaptic junction. If gabapentin does indeed increase GABA levels or the effectiveness of GABA at the synaptic junction, then it could be classified as a GABA-mimetic and might decrease or inhibit cerebral function and might, therefore, slow function and decrease mood leading to depression.

The fact that a GABA agonist or GABA-mimetic might work just the opposite way by increasing mood and thus, be an antidepressant, is a new concept, different from the prevailing opinion of GABA activity heretofore.

The compounds of the instant invention are also expected to be useful in the treatment of anxiety and of panic as demonstrated by means of standard pharmacological procedures.

MATERIAL AND METHODS

Carrageenin-Induced Hyperalgesia

Nociceptive pressure thresholds were measured in the rat paw pressure test using an analgesymeter (Randall-Sellitto Method: Randall L.O., Sellitto J.J., A method for measurement of analgesic activity on inflamed tissue. Arch. Int. Pharmacodyn., 4:409-419 (1957)). Male Sprague-Dawley rats (70-90 g) were trained on this apparatus before the test day. Pressure was gradually applied to the hind paw of each rat and nociceptive thresholds were determined as the pressure (g) required to elicit paw withdrawal. A cutoff point of 250 g was used to prevent any tissue damage to the paw. On the test day, two to three baseline measurements were taken before animals were administered 100 µL of 2% carrageenin by intraplantar injection into the right hind paw. Nociceptive thresholds were taken again 3 hours after carrageenin to establish that animals were exhibiting hyperalgesia. Animals were dosed with either gabapentin (3-300 mg/kg, s.c.), morphine (3 mg/kg, s.c.), or saline at 3.5 hours after carrageenin and nociceptive thresholds were examined at 4, 4.5, and 5 hours post carrageenin.

Semicarbazide-Induced Tonic Seizures

Tonic seizures in mice are induced by subcutaneous administration of semicarbazide (750 mg/kg). The latency to the tonic extension of forepaws is noted. Any mice not convulsing within 2.0 hours after semicarbazide are considered protected and given a maximum latency score of 120 minutes.

Animals

Male Hooded Lister rats (200-250 g) are obtained from Interfauna (Huntingdon, UK) and male TO mice (20-25 g) are obtained from Bantin and Kingman (Hull, UK). Both rodent species are housed in groups of six. Ten

Common Marmosets (Callithrix Jacchus) weighing between 280 and 360 g, bred at Manchester University Medical School (Manchester, UK) are housed in pairs. All animals are housed under a 12-hour light/dark cycle (lights on at 07.00 hour) and with food and water ad libitum.

Drug Administration

Drugs are administered either intraperitoneally (IP) or subcutaneously (SC) 40 minutes before the test in a volume of 1 mL/kg for rats and marmosets and 10 mL/kg for mice.

Mouse Light/Dark Box

The apparatus is an open-topped box, 45 cm long, 27 cm wide, and 27 cm high, divided into a small (2/5) and a large (3/5) area by a partition that extended 20 cm above the walls (Costall B., et al., Exploration of mice in a black and white box: validation as a model of anxiety. Pharmacol. Biochem. Behav., 32:777-785 (1989)).

There is a 7.5 × 7.5 cm opening in the center of the partition at floor level. The small compartment is painted black and the large compartment white. The white compartment is illuminated by a 60-W tungsten bulb. The laboratory is illuminated by red light. Each mouse is tested by placing it in the center of the white area and allowing it to explore the novel environment for 5 minutes. The time spent in the illuminated side is measured (Kilfoil T., et al., Effects of anxiolytic and anxiogenic drugs on exploratory activity in a simple model of anxiety in mice. Neuropharmacol., 28:901-905 (1989)).

Rat Elevated X-Maze

A standard elevated X-maze (Handley S.L., et al., Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of 'fear'-motivated behavior. Naunyn-Schiedeberg's Arch. Pharmacol., 327:1-5 (1984)), was automated as previously described (Field, et al., Automation of the rat elevated X-maze test of anxiety. Br. J. Pharmacol., 102(Suppl):304P (1991)). The animals are placed on the center of the X-maze facing one of the open arms. For determining anxiolytic effects the entries and time spent on the end half sections

of the open arms is measured during the 5-minute test period (Costall, et al., Use of the elevated plus maze to assess anxiolytic potential in the rat. Br. J. Pharmacol., 96(Suppl):312P (1989)).

Marmoset Human Threat Test

The total number of body postures exhibited by the animal towards the threat stimulus (a human standing approximately 0.5 m away from the marmoset cage and staring into the eyes of the marmoset) is recorded during the 2-minute test period. The body postures scored are slit stares, tail postures, scent marking of the cage/perches, piloerection, retreats, and arching of the back. Each animal is exposed to the threat stimulus twice on the test day before and after drug treatment. The difference between the two scores is analyzed using one-way analysis of variance followed by Dunnett's t-test. All drug treatments are carried out SC at least 2 hours after the first (control) threat. The pretreatment time for each compound is 40 minutes.

Rat Conflict Test

Rats are trained to press levers for food reward in operant chambers. The schedule consists of alternations of four 4-minute unpunished periods on variable interval of 30 seconds signaled by chamber lights on and three 3-minute punished periods on fixed ratio 5 (by footshock concomitant to food delivery) signaled by chamber lights off. The degree of footshock is adjusted for each rat to obtain approximately 80% to 90% suppression of responding in comparison with unpunished responding. Rats receive saline vehicle on training days.

The compounds of the instant invention are also expected to be useful in the treatment of pain and phobic disorders (Am. J. Pain Manag., 5:7-9 (1995)).

The compounds of the instant invention are also expected to be useful in treating the symptoms of manic, acute or chronic, single upside, or recurring depression. They are also expected to be useful in treating and/or preventing bipolar disorder (United States Patent Number 5,510,381).

TNBS-Induced Chronic Visceral Allodynia In Rats

Injections of trinitrobenzene sulfonic (TNBS) into the colon have been found to induce chronic colitis. In human, digestive disorders are often associated with visceral pain. In these pathologies, the visceral pain threshold is decreased indicating a visceral hypersensitivity. Consequently, this study was designed to evaluate the effect of injection of TNBS into the colon on visceral pain threshold in a experimental model of colonic distension.

Animals and Surgery

Male Sprague-Dawley rats (Janvier, Le Genest-St-Ilse, France) weighing 340-400 g are used. The animals are housed 3 per cage in a regulated environment (20 ± 1°C, 50 ± 5% humidity, with light 8:00 am to 8:00 pm). Under anesthesia (ketamine 80 mg/kg i.p; acepromazin 12 mg/kg ip), the injection of TNBS (50 mg/kg) or saline (1.5 mL/kg) is performed into the proximal colon (1 cm from the cecum). After the surgery, animals are individually housed in polypropylene cages and kept in a regulated environment (20 ± 1°C, 50 ± 5% humidity, with light 8:00 am to 8:00 pm) during 7 days.

Experimental Procedure

At Day 7 after TNBS administration, a balloon (5-6 cm length) is inserted by anus and kept in position (tip of balloon 5 cm from the anus) by taping the catheter to the base of the tail. The balloon is progressively inflated by step of 5 mm Hg, from 0 to 75 mm Hg, each step of inflation lasting 30 seconds. Each cycle of colonic distension is controlled by a standard barostat (ABS, St-Dié, France). The threshold corresponds to the pressure which produced the first abdominal contraction and the cycle of distension is then discontinued. The colonic threshold (pressure expressed in mm Hg) is determined after performance of four cycles of distension on the same animal.

Determination of the Activity of the Compound

Data is analyzed by comparing test compound-treated group with TNBS-treated group and control group. Mean and sem are calculated for each group. The antiallodynic activity of the compound is calculated as follows:

Activity (%) = (group C – group T) / (group A – group T)

Group C: mean of the colonic threshold in the control group

Group T: mean of the colonic threshold in the TNBS-treated group

Group A: mean of the colonic threshold in the test compound-treated group

Statistical Analysis

Statistical significance between each group was determined by using a one-way ANOVA followed by Student's unpaired t-test. Differences were considered statistically significant at $p < 0.05$.

Compounds

TNBS is dissolved in EtOH 30% and injected under a volume of 0.5 mL/rat. TNBS is purchased from Fluka.

Oral administration of the test compound or its vehicle is performed 1 hour before the colonic distension cycle.

Sub-cutaneous administration of the test compound or its vehicle is performed 30 minutes before the colonic distension cycle.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more

substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

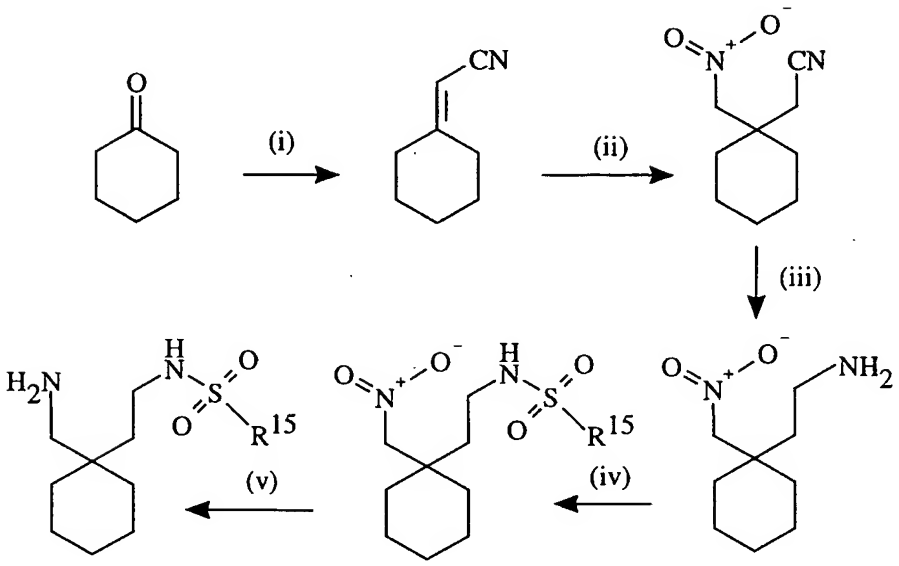
The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 1 g according to the particular application and the potency of the active component. In medical use the drug may be administered three times daily as, for example, capsules of 100 or 300 mg. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 100 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Sulfonamides of the instant invention can be synthesized by the general route outlined in Scheme 1.

Scheme 1



Reagents:

(i) Diethylcyanomethyl phosphonate, NaH, tetrahydrofuran;

(ii) Nitromethane, tetrabutylammonium fluoride, tetrahydrofuran;

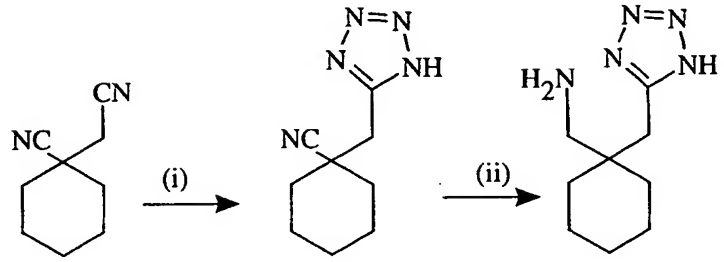
(iii) Borane methyl sulphide, toluene;

(iv) Triethylamine, $R^{15}SO_2Cl$, tetrahydrofuran;

(v) 10% Pd-C, hydrogen gas, methanol.

Tetrazoles can be synthesized by the general route outlined in Scheme 2.

Scheme 2



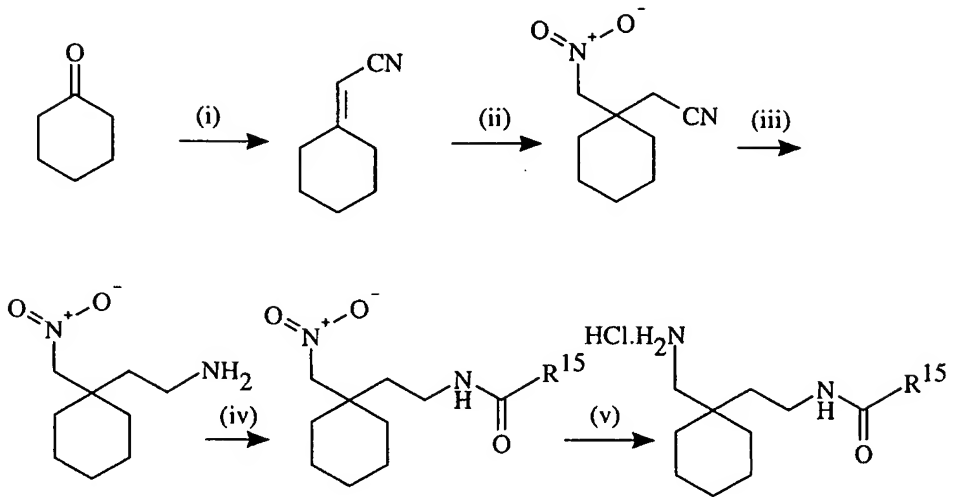
Reagents:

(i) Trimethylsilylazide, Trimethylaluminium (2M in hexanes), toluene;

(ii) Raney Nickel, Methanol.

Amides can be synthesized by the general route outlined in Scheme 3.

Scheme 3



Reagents:

(i) Diethylcyanomethyl phosphonate, NaH, tetrahydrofuran;

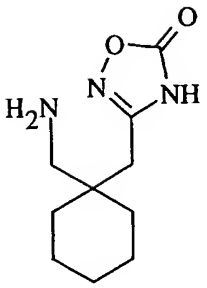
(ii) Nitromethane, tetrabutylammonium fluoride, tetrahydrofuran;

(iii) Borane methyl sulphide, toluene;

(iv) Triethylamine, $R^{15}COCl$, tetrahydrofuran;

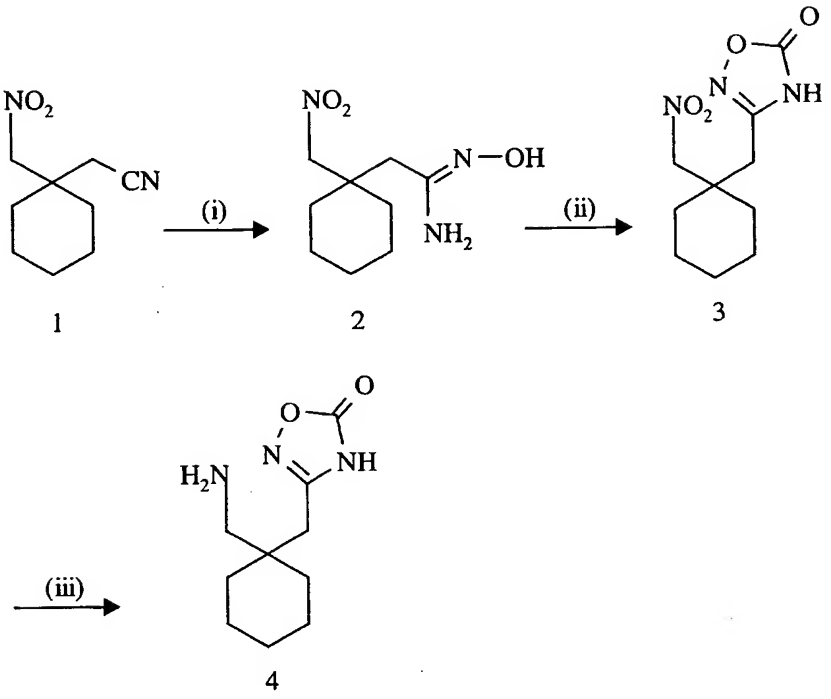
(v) 10% Pd-C, hydrogen gas, methanol.

Heterocycles such as



can be synthesized by the general route outlined in Scheme 4.

Scheme 4



(i) $NH_2OH{\cdot}HCl$, Et_3N;

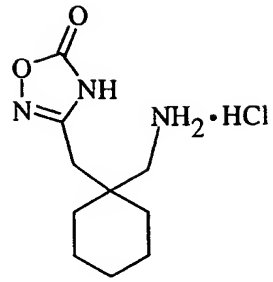
(ii) iBuOCOCl, pyridine followed by reflux in xylene;

(iii) Fe/HCl.

Compound 1 [(1-Nitromethyl-cyclohexyl)acetonitrile] can be treated with hydroxylamine hydrochloride in the presence of a base such as triethylamine to give compound 2.

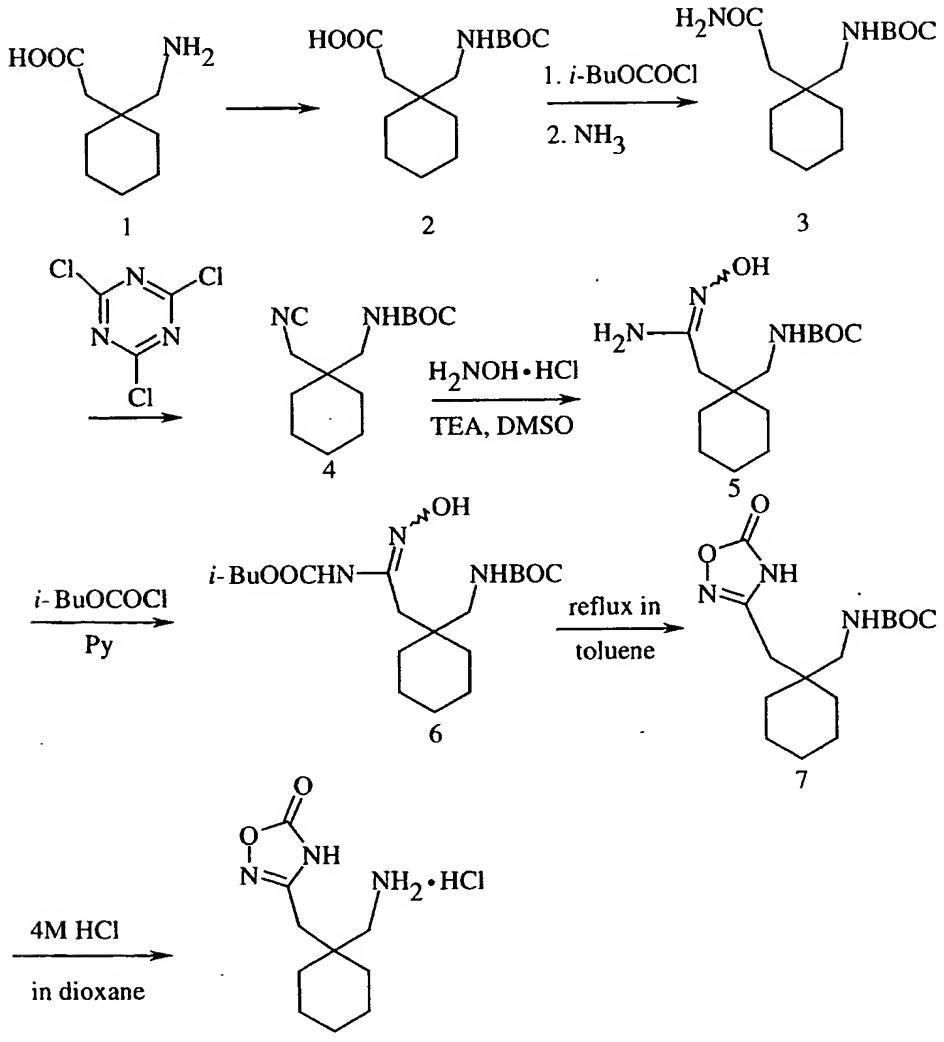
The heterocyclic compound 3 can be prepared from compound 2 by treatment with iso-butyl chloroformate in the presence of a base such as pyridine followed by reflux in a solvent such as xylene. The nitro compound (compound 3) can be converted to the required amine by reduction, for example, with iron and hydrochloric acid.

Heterocycles such as

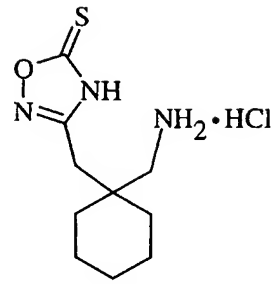


can be synthesized by the general route outlined in Scheme 5a.

Scheme 5a



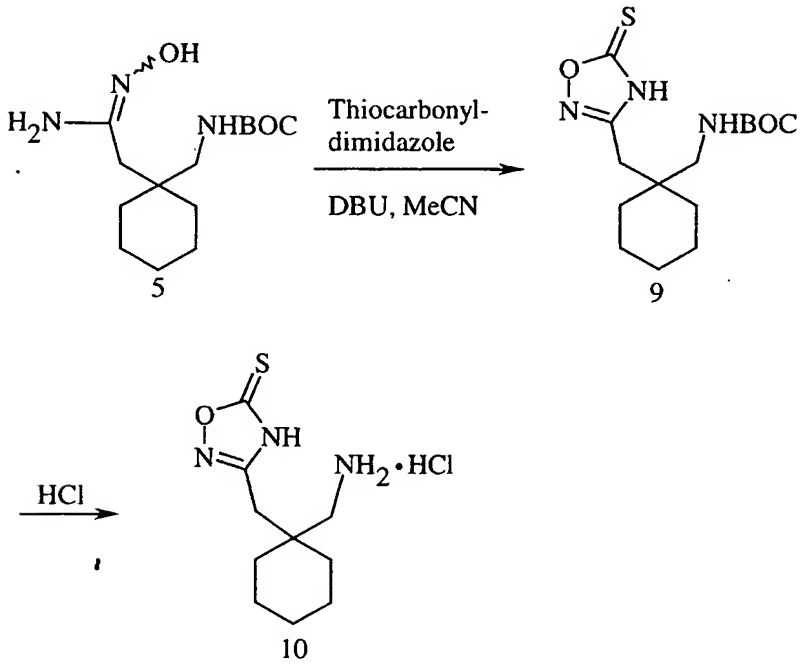
Heterocycles such as



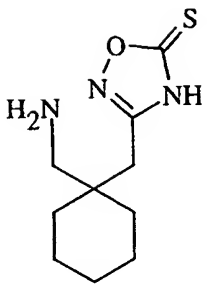
10

can be synthesized by the general route outlined in Scheme 5b.

Scheme 5b

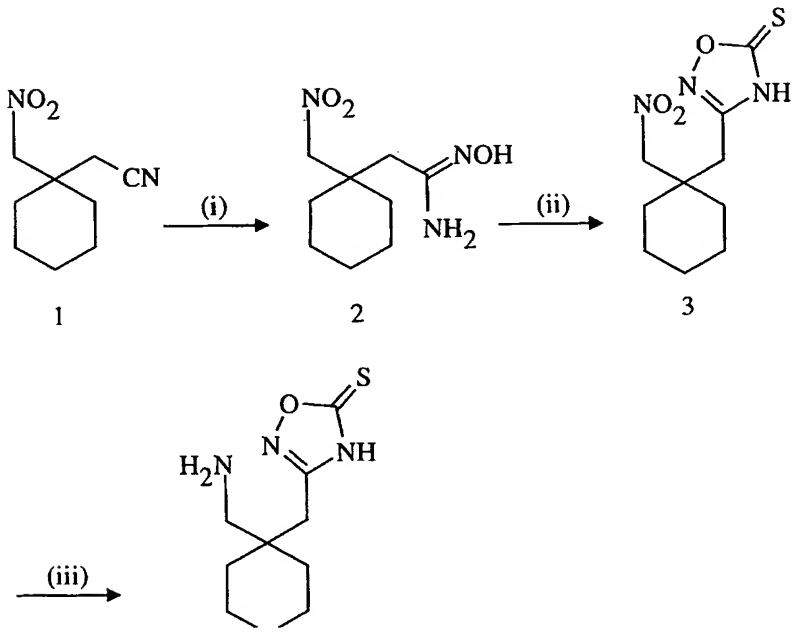


Heterocycles such as



can be synthesized by the general route shown in Scheme 6 below:

Scheme 6



(i) $NH_2OH \cdot HCl$, Et_3N;

(ii) 1,1′-thiocarbonyldiimidazole followed by DBU or DBN;

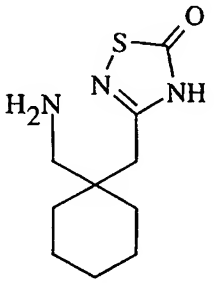
(iii) Fe/HCl.

Compound 1 [(Nitromethyl-cyclohexyl)acetonitrile] can be treated with hydroxylamine hydrochloride in the presence of a base such as triethylamine to give compound 2.

The heterocyclic compound 3 can be prepared from compound 2 by treatment with 1,1′-thiocarbonyldiimidazole followed by a base such as 1,8-diazabicyclo-[4,5,0]-undec-7-ene (DBU) or 1,5-diazabicyclo[2.2.2]octane] (DBN).

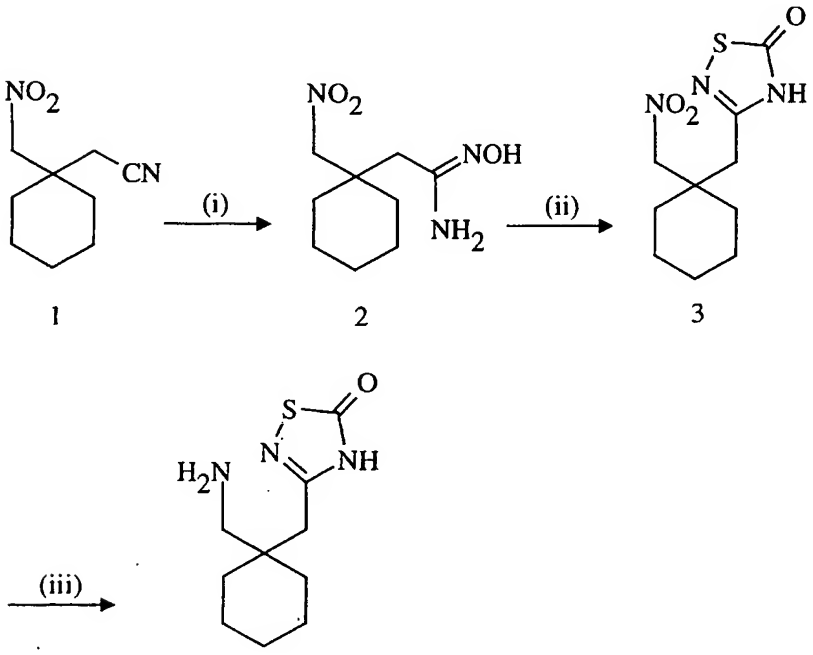
The nitro compound (compound 3) can be converted to the required amine by reduction, for example, with iron and hydrochloric acid.

Heterocycles such as



can be synthesized following the general route as shown in Scheme 7.

Scheme 7



(i) $NH_2OH \cdot HCl$, Et_3N;

(ii) 1,1′-thiocarbonyldiimidazole followed by silica gel or $BF_3 \cdot OEt_2$;

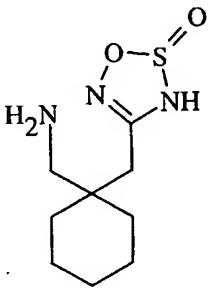
(iii) Fe/HCl.

Compound 1 [(Nitromethyl-cyclohexyl)acetonitrile] can be treated with hydroxylamine hydrochloride in the presence of a base such as triethylamine to give compound 2.

The heterocyclic compound 3 can be prepared from compound 2 by treatment with 1,1′-thiocarbonyldiimidazole followed by treatment with silica gel or boron trifluoride etherate.

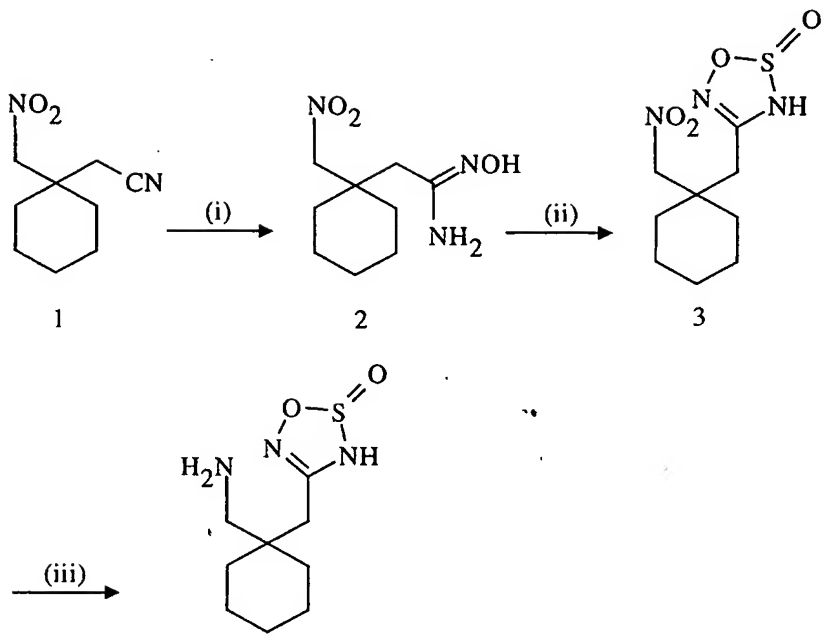
The nitro compound (compound 3) can be converted to the required amine by reduction, for example, with iron and hydrochloric acid.

Heterocycles such as



can be synthesized following the general route outlined in Scheme 8:

Scheme 8



(i) $NH_2OH \cdot HCl$, Et_3N;

(ii) Pyridine, $SOCl_2$;

(iii) Fe/HCl.

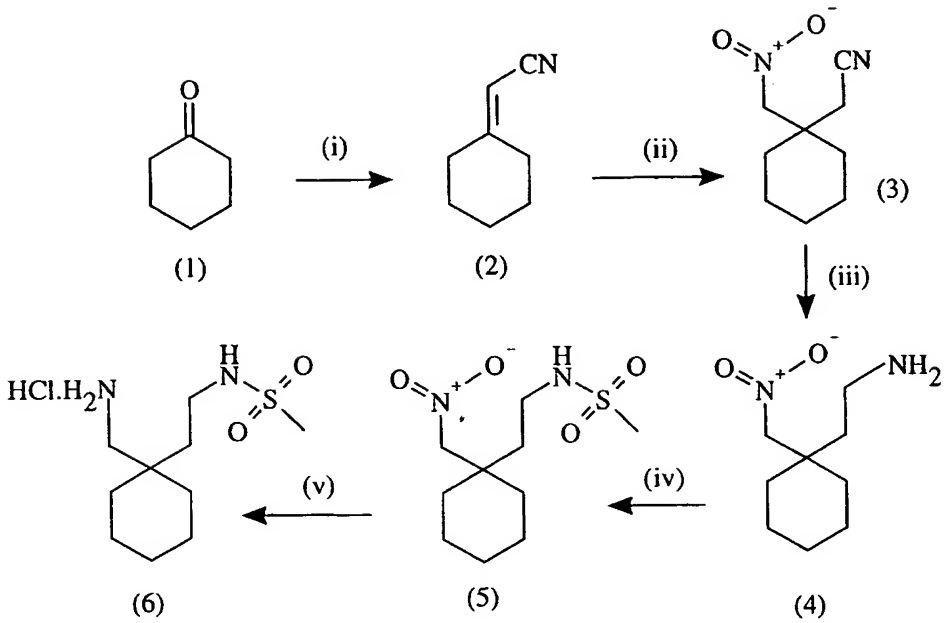
Compound 1 [(Nitromethyl-cyclohexyl)acetonitrile] can be treated with hydroxylamine hydrochloride in the presence of a base such as triethylamine to give compound 2.

The heterocyclic compound 3 can be prepared from compound 2 by treatment with thionyl chloride in the presence of a base such as pyridine.

The nitro compound (compound 3) can be converted to the required amine by reduction, for example, with iron and hydrochloric acid.

The following examples are illustrative of the instant invention; they are not intended to limit the scope.

EXAMPLE 1



Reagents:

(i) Diethylcyanomethyl phosphonate, NaH, tetrahydrofuran;

(ii) Nitromethane, tetrabutylammonium fluoride, tetrahydrofuran;

(iii) Borane methyl sulphide, toluene;

(iv) Triethylamine, methanesulphonyl chloride, tetrahydrofuran;

(v) 10% Pd-C, hydrogen gas, methanol then HCl.

Cyclohexylidene-acetonitrile (2)

Sodium hydride (60% in oil, 0.80 g, 20 mmol) was suspended in 50 mL tetrahydrofuran and chilled in ice under nitrogen. Diethylcyanomethyl phosphonate (3.85 g, 22 mmol) was added dropwise in 10 mL tetrahydrofuran and stirring continued for 15 minutes to give a clear solution. Cyclohexanone (1.90 g, 19 mol) was added in 5 mL tetrahydrofuran and the reaction mixture allowed to warm up to room temperature. The liquor was decanted and the residue washed three times with ether. The liquor and washings were combined, washed with dilute hydrochloric acid and water, dried over magnesium sulphate, filtered, and evaporated to dryness. The residue was purified by chromatography on silica

eluting with heptane/ethyl acetate 4:1 to give the required product as a colorless oil (1.5 g, 67%).

^{1}H NMR 400 MHz ($CDCl_3$): δ 1.50 (m, 6H), 2.25 (t, J = 5.6 Hz, 2H), 2.49 (t, J = 6.8 Hz, 2H), 5.04 (s, 1H).

IR vmax 2933, 2859, 2217, 1633, 1449

(1-Nitromethyl-cyclohexyl)-acetonitrile (3)

The nitrile (compound 2, 0.78 g, 6.44 mmol), nitromethane (0.80 g, 13.11 mmol) and tetrabutyl ammonium fluoride (1.0 M in tetrahydrofuran, 10 mL, 10 mmol) were heated in 20 mL tetrahydrofuran to 70°C overnight. The reaction mixture was diluted with ethyl acetate and washed with dilute hydrochloric acid and water, dried over magnesium sulphate, filtered, and evaporated to dryness. The residue was purified by chromatography on silica eluting with heptane/ethyl acetate 3:1 to give the required product as a yellow oil (0.83 g, 71%).

^{1}H NMR 400 MHz ($CDCl_3$): δ 1.57 (s, 10H), 2.63 (s, 2H), 4.52 (s, 2H).

Analysis calculated for $C_9H_{13}N_2O_2$:

C, 59.32; H, 7.74; N, 15.37.

Found: C, 59.40; H, 7.65; N, 15.18.

2-(1-Nitromethyl-cyclohexyl)-ethylamine (4)

Borane methyl sulphide (2.0 M in toluene, 1.3 mL, 2.6 mmol) was added to compound 3 (0.4 g, 2.2 mmol) in toluene (10 mL) under nitrogen. After heating to 60°C for 3 hours, the mixture was allowed to cool, and 15 mL methanol was added followed by 15 mL 4 M HCl in dioxan. After reflux for 1 hour, the mixture was evaporated to dryness. Crystallization from ethyl acetate gave the required product as colorless crystals (0.23 g, 47%); mp 170-173°C.

^{1}H NMR 400 MHz (d_6-DMSO): δ 1.30-1.50 (m, 10H), 1.64-1.69 (m, 2H), 2.82-2.86 (m, 2H), 4.57 (s, 2H), 7.89 (s, 3H).

Analysis calculated for $C_9H_{18}N_2O_2 \cdot HCl \cdot 0.2H_2O$:

C, 47.77; H, 8.64: N, 12.38.

Found: C, 47.80; H, 8.66; N, 12.64.

N-[2-(1-Nitromethyl-cyclohexyl)-ethyl]-methanesulfonamide (5)

Triethylamine (0.64 g, 6.3 mmol) was added dropwise to a mixture of the amine hydrochloride salt (compound 4, 0.70 g, 3.1 mmol) and methane sulfonyl chloride (0.36 g, 6.3 mmol) in tetrahydrofuran (35 mL). After stirring at room temperature for 2 hours, the mixture was filtered, diluted with ethyl acetate, and washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water, dried over magnesium sulphate, filtered, and evaporated to dryness. The residue was crystallized from ethyl acetate/heptane to give colorless crystals (0.39 g, 47%); mp 86-88°C.

^{1}H NMR 400 MHz (d_6-DMSO): δ 1.35-1.50 (m, 10H), 1.55-1.60 (m, 2H), 2.89 (s, 3H), 2.99-3.06 (m, 2H), 4.55 (s, 2H), 6.93 (t, J = 6 Hz, 1H).

Analysis calculated for $C_{10}H_{20}N_2O_4S$:

C, 45.44; H, 7.63; N, 10.60; S, 12.13.

Found: C, 45.77; H, 7.64; N, 10.58; S, 12.17.

N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-methanesulfonamide hydrochloride (6)

Ten percent Palladium on carbon was added under nitrogen to a solution of compound 5 (0.35 g, 1.3 mmol) in methanol (50 mL). The mixture was shaken under 40 psi hydrogen for 6 hours and then filtered through keiselguhr. The filtrate was evaporated to dryness. 4N HCl in dioxan was added followed by ether to give the product as a colorless crystalline solid (0.33 g, 92%); mp 196-199°C.

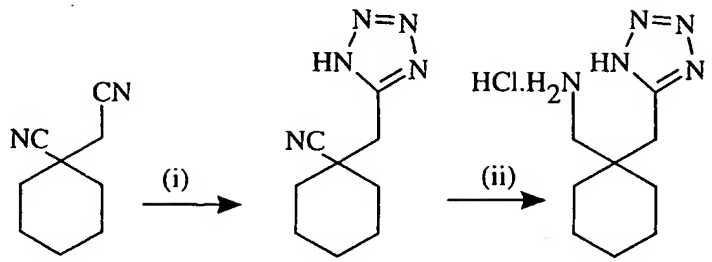
^{1}H NMR 400 MHz (d_6-DMSO): δ 1.25-1.45 (m, 10H), 1.55-1.60 (m, 5H), 2.70-2.75 (m, 2H), 2.90-2.95 (m, 5H), 6.86 (t, J = 6.0 Hz, 1H), 7.86 (bs, 3H).

Analysis calculated for $C_{10}H_{22}N_2O_2S \cdot HCl \cdot 0.25H_2O$:

C, 43.63; H, 8.60; N, 10.17.

Found: C, 43.43; H, 8.64; N, 9.95.

EXAMPLE 2



(1) (2) (3)

Reagents:

(i) Trimethylsilylazide, trimethylaluminium (2 M in hexanes), toluene;

(ii) Raney Nickel, hydrogen gas, methanol then HCl.

1-(1H-Tetrazol-5-ylmethyl)-cyclohexanecarbonitrile (2)

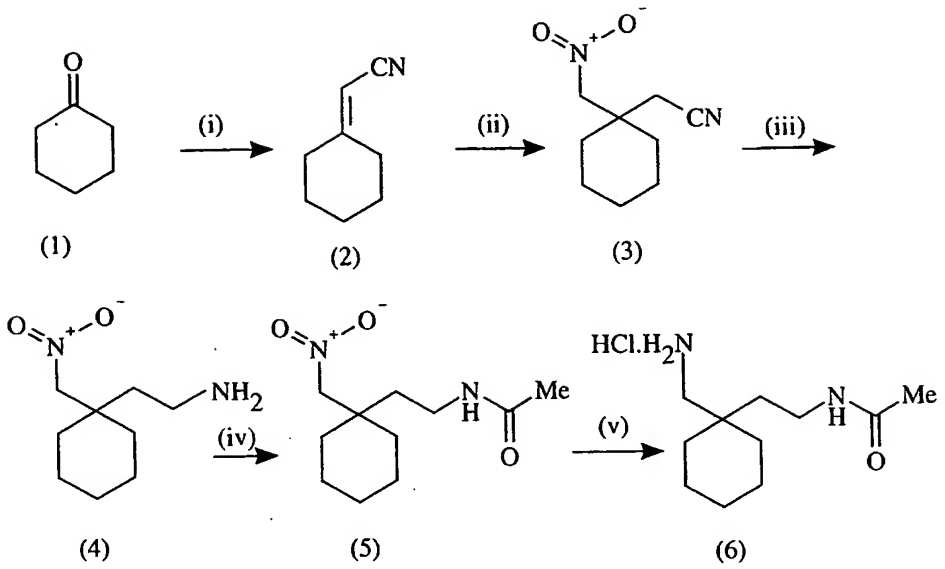
To a soluton of the bis nitrile (Griffiths G., Mettler H., Mills L.S., and Previdoli F., Helv. Chim. Acta, 74:309 (1991)) (1.48 g, 10 mmol) in toluene (20 mL) under nitrogen was added trimethylsilylazide (1.15 g, 10 mmol) followed by trimethylaluminium (5 mL, 2.0 M in hexanes, 10 mmol). After heating to 90°C overnight, the mixture was allowed to cool and added carefully to ethyl acetate, ice and 6N hydrochloric acid. The aqueous phase was extracted with ethyl acetate, and the extracts washed with water, dried over magnesium sulphate, and evaporated to dryness. Crystallization gave the required compound (158 mg, 8%).

C-[1-(1H-Tetrazol-5-ylmethyl)-cyclohexyl]-methylamine hydrochloride (3)

The tetrazole (compound 8, 158 mg, 0.83 mmol) in methanol was added to a washed suspension of Raney nickel in methanol. The mixture was shaken under 40 psi hydrogen for 3.5 hours and then filtered to remove the catalyst and evaporated to dryness. The residue was partitioned between ethyl acetate and dilute hydrochloric acid. The aqueous phase was separated and evaporated to dryness. Recrystallization from methanol/ether gave the required product (44 mg, 23%); mp 176-179°C.

^{1}H NMR 400 MHz (d_6-DMSO): δ 1.20-1.60 (m, 10H), 2.84 (s, 2H), 3.07 (s, 2H), 8.06 (bs, 3H).

EXAMPLE 3



Reagents:

(i) Diethylcyanomethyl phosphonate, NaH, tetrahydrofuran;

(ii) Nitromethane, tetrabutylammonium fluoride, tetrahydrofuran;

(iii) Borane methyl sulphide, toluene;

(iv) Triethylamine, acetyl chloride, tetrahydrofuran;

(v) 10% Pd-C, hydrogen gas, methanol then HCl

Cyclohexylidene-acetonitrile (2)

Sodium hydride (60% in oil, 0.80 g, 20 mmol) was suspended in 50 mL tetrahydrofuran and chilled in ice under nitrogen. Diethylcyanomethyl phosphonate (3.85 g, 22 mmol) was added dropwise in 10 mL tetrahydrofuran and stirring continued for 15 minutes to give a clear solution. Cyclohexanone (1.90 g, 19 mmol) was added in 5 mL tetrahydrofuran and the reaction mixture allowed to warm up to room temperature. The liquor was decanted and the residue washed three times with ether. The liquor and washings were combined, washed with dilute hydrochloric acid and water, dried over magnesium sulphate, filtered, and evaporated to dryness. The residue was purified by chromatography on silica eluting with heptane/ethyl acetate 4:1 to give the required product as a colorless oil (1.5 g, 67%).

^{1}H NMR 400 MHz ($CDCl_3$): δ 1.50 (m, 6H), 2.25 (t, J = 5.6 Hz, 2H), 2.49 (t, J = 6.8 Hz, 2H), 5.04 (s, 1H).

IR νmax 2933, 2859, 2217, 1633, 1449.

(1-Nitromethyl-cyclohexyl)-acetonitrile (3)

The nitrile (compound 2, 0.78 g, 6.44 mmol), nitromethane (0.80 g, 13.11 mmol) and tetrabutyl ammonium fluoride (1.0 M in tetrahydrofuran, 10 mL, 10 mmol) were heated in 20 mL tetrahydrofuran to 70°C overnight. The reaction mixture was diluted with ethyl acetate and washed with dilute hydrochloric acid and water, dried over magnesium sulphate, filtered, and evaporated to dryness. The residue was purified by chromatography on silica eluting with heptane/ethyl acetate 3:1 to give the required product as a yellow oil (0.83 g, 71%).

^{1}H NMR 400 MHz ($CDCl_3$): δ 1.57 (s, 10H), 2.63 (s, 2H), 4.52 (s, 2H).

Analysis calculated for $C_9H_{13}N_2O_2$:

C, 59.32; H, 7.74; N, 15.37.

Found: C, 59.40; H, 7.65; N, 15.18.

2-(1-Nitromethyl-cyclohexyl)-ethylamine (4)

Borane methyl sulphide (2.0 M in toluene, 1.3 mL, 2.6 mmol) was added to compound 3 (0.4 g, 2.2 mmol) in toluene (10 mL) under nitrogen. After heating to 60°C for 3 hours, the mixture was allowed to cool, and 15 mL methanol was added followed by 15 mL 4 M HCl in dioxan. After reflux for 1 hour, the mixture was evaporated to dryness. Crystallization from ethyl acetate gave the required product as colorless crystals (0.23 g, 47%); mp 170-173°C.

^{1}H NMR 400 MHz (d_6-DMSO): δ 1.30-1.50 (m, 10H), 1.64-1.69 (m, 2H), 2.82-2.86 (m, 2H), 4.57 (s, 2H), 7.89 (s, 3H).

Analysis calculated for $C_9H_{18}N_2O_2 \cdot HCl \cdot 0.2H_2O$:

C, 47.77; H, 8.64; N, 12.38.

Found: C, 47.80; H, 8.66; N, 12.64.

N-[2-(1-Nitromethyl-cyclohexyl)-ethyl]-acetamide (5)

The amine hydrochloride salt (compound 4, 0.50 g, 2.25 mmol) was reacted with acetyl chloride (0.20 g, 2.55 mmol) and triethylamine (0.45 g, 4.45 mmol) in tetrahydrofuran following the procedure described in Example 1, Step 4. Purification by chromatography on silica eluting with ethyl acetate gave the required product as a crystalline solid (0.35 g, 69%); mp 68-70°C.

^{1}H NMR 400 MHz ($CDCl_3$): δ 1.40-1.60 (m, 10H), 1.60-1.65 (m, 2H), 1.98 (s, 3H), 3.30-3.40 (m, 2H), 4.40 (s, 2H), 5.59 (bs, 1H).

N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-acetamide hydrochloride (6)

Compound 5 (0.30 g, 1.3 mmol) was hydrogenated in the presence of 10% palladium on carbon following the procedure described in Example 1, Step 5 to give the product as the hydrochloride salt (0.35 g, 100%).

^{1}H NMR 400 MHz (d_6-DMSO): δ 1.20-1.40 (m, 10H), 1.40-1.50 (m, 2H), 1.81 (s, 3H), 2.75 (q, J = 6.0 Hz, 2H), 2.95-3.05 (m, 2H), 7.99 (bs, 3H), 8.06 (t, J = 4.8 Hz, 1H).

IR νmax 3265, 2929, 1628, 1553, 1446, 1373, 1298.

EXAMPLE 4

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one; hydrochloride

[1-(tert-Butoxycarbonylamino-methyl)-cyclohexyl]-acetic acid (2)

A solution of Gabapentin (**1**) (9.37g, 0.0547 mol) in 125 mL 1N NaOH and 50 mL THF was cooled to 0°C and a solution of di-tert-butyl dicarbonate (13.1 g, 0.06 mol) in 200 mL THF was slowly added. The reaction mixture was stirred at room temperature 2 hours and concentrated on a rotary evaporator to remove THF. The concentrate was saturated with KH_2PO_4 and extracted 3X EtOAc. The EtOAc extracts were washed 2X brine and dried over $MgSO_4$. Evaporation yielded 14.8 g (100%) white solid, mp 109-111°C.

^{1}HNMR ($CDCl_3$) δ 1.2-1.4 (m, 19H), 2.27 (s, 2H), 3.11 (d, 2H, J = 6.84 Hz), 4.95 (broad, 1H).

MS (APCI) m/z 272 (M + 1).

Analysis calculated for $C_{14}H_{25}NO_4$:

C, 61.97; H, 9.29; N, 5.16.

Found: C, 62.36; H, 9.27; N, 5.19.

(1-Carbamoylmethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (3)

[1-(tert-Butoxycarbonylamino-methyl)-cyclohexyl]-acetic acid (**2**) (152 g, 0.56 mol) was taken up in 1 L THF and triethylamine (66.2 g, 0.65 mol) and cooled to -10°C. Over a 1-hour period, isobutyraldehyde was added (84.7 g, 0.62 mol), and the heterogeneous mixture was stirred at 0°C for 15 minutes. Ammonia gas was bubbled into the cold reaction mixture for 30 minutes, and the mixture was allowed to warm to room temperature. After 16 hours stirring, the reaction mixture was evaporated to dryness on a rotary evaporator, and the residue was taken up in water, extracted 3X EtOAc, washed 2X brine and dried over $MgSO_4$. Evaporation yielded an oil which was crystallized from pentane to yield 116.5 g (77%) white crystals; mp 123-125°C.

^{1}HNMR ($CDCl_3$) δ 1.2-1.6 (m, 19H), 2.12 (s, 2H), 3.13 (d, 2H, J = 7.08 Hz), 4.97 (s, IH), 5.43 (s, 1H), 7.34 (s, 1H).

MS (APCI) 271 m/z. (M +1).

Analysis calculated for $C_{14}H_{26}N_2O_3$:

C, 62.19; H, 9.69; N, 10.36.

Found: C, 62.00; H, 9.72; N, 9.96.

(1-Cyanomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (4)

Cyanuric chloride (39.5 g, 0.214 mol) was added to (1-carbamoylmethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (**3**) (116 g, 0.429 mol) in 400 mL DMF. An ice-water bath was used to moderate the exotherm, and the reaction mixture was stirred at room temperature for 1.5 hours. The mixture was poured into ice-water containing 120 g (1.43 mol) $NaHCO_3$ and was extracted 4X EtOAc. The extracts were washed 1X water, 2X brine and dried over Na_2SO_4. Evaporation yielded an oil which was taken up in 3:1 hexane/EtOAc and filtered through silica gel. Evaporation yielded white crystals (86.5 g, 80%); mp 54-58°C.

^{1}HNMR ($CDCl_3$) δ 1.3-1.5 (m, 19H), 2.30 (s, 2H), 3.15 (d, 2h, J = 7.00 Hz), 4.60 (broad, 1H).

MS (APCI) m/z 253 (M + 1).

Analysis calculated for $C_{14}H_{24}N_2O_2$:

C, 66.63; H, 9.59; N, 11.10.

Found: C, 66.64; H, 9.52; N, 10.80.

[1-(N-Hydroxycarbamimidoylmethyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (5)

A suspension of hydroxylamine hydrochloride (69.5 g, 1.00 mol) in DMSO (300 mL) was cooled in ice-water, and triethylamine (106.7 g, 1.05 mol) was added. The resulting exotherm brought the temperature to 20°C. The mixture was stirred at this temperature 15 minutes, and triethylamine hydrochloride was filtered off and washed with THF. The filtrate was concentrated to remove THF, and (1-cyanomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (4) (50.4 g, 0.2 mol) was added, and the mixture was heated at 75°C for 15 hours. After cooling, the reaction mixture was diluted with water (1 L) and extracted 3X EtOAc. The EtOAc extracts were washed 1X saturated KH_2PO_4, 1X saturated $NaHCO_3$, 2X brine and dried over Na_2SO_4. Evaporation yielded a gummy solid which was triturated in Et_2O to give white crystals, 25.2 g (44%); mp 125-127°C.

^{1}HNMR ($CDCl_3$) δ 1.3-1.5 (m 19H), 1.99 (s, 2H), 3.12 (d, 2H J = 6.84 Hz), 4.93 (t, 1H, J = 6.84 Hz), 5.40 (s, 1H).

MS (APCI) m/z 286 (M + 1).

Analysis calculated for $C_{14}H_{27}N_3O_3$:

C, 58.92; H, 9.54; N, 14.72.

Found: C, 58.96; H, 9.80; N, 14.65.

BOC-Gabapentin amidoxime carbamate (6)

A solution of [1-(N-Hydroxycarbamimidoylmethyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (5) (25.1 g, 0.088 mol) and pyridine (7.82 g, 0.099 mol) in DMF (200 mL) was cooled in ice-water as isobutyraldehyde (12.32 g, 0.09 mol) was added dropwise. After 15 minutes, the bath was removed

and the mixture was stirred at room temperature 2 hours, diluted with water, and extracted 3X EtOAc. The extracts were washed 1X water, 2X brine and dried over Na_2SO_4. Evaporation yielded an oil, 34 g (100%) which was used without further purification.

MS (APCI) m/z 386 (M + 1).

[1-(5-Oxo-4,5-dihydro-[1,2,4]oxadiazol-3-ylmethyl)-cyclohexylmethyl]-carbamic acid tert-butyl (7)

BOC-Gabapentin amidoxime carbamate (33.88 g, 0.088 mol) was taken up in xylene (250 mL) and heated under reflux 2.5 hours. The xylene was evaporated off and the residue taken up in Et_2O and extracted 3X 75 mL 1N NaOH. The alkaline extracts were acidified with saturated KH_2PO_4 and extracted 3X Et_2O. The Et_2O extracts were washed 1X saturated KH_2PO_4, 2X brine and dried over Na_2SO_4. Evaporation yielded 17.9 g (65%) of a cream-colored solid, mp 140-143°C.

^{1}HNMR ($CDCl_3$) δ 1.0-1.6 (m, 19H), 2.42 (s, 2H), 3.00 (d, 2H, J = 7.32 Hz), 4.86 (t, 1H, J = 7.08 Hz), 11.30 (s, 1H).

MS (APCI) m/z 312 (M + 1).

Analysis calculated for $C_{15}H_{25}N_3O_4$:

C, 57.86; H, 8.09; N, 13.49.

Found: C, 58.21; H, 8.31; N, 13.30.

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one; hydrochloride (8)

A solution of BOC-Gabapentin oxadiazolone (17.7 g, 0.0568 mol) in 4 M HCl in dioxane (200 mL) was allowed to stand 1.5 hours. Concentration to half volume followed by addition of Et_2O gave a precipitate which was filtered off and recrystallized from MeOH to give white crystals (12.98 g, 92.7%), mp 209-212°C.

^{1}HNMR (DMSO-d_6) δ 1.2-1.5 (m, 10H), 2.64 (s, 4H), 2.79 (s, 2H), 7.98 (s, 3H), 12.35 (s, 1H).

MS (APCI) m/z 212 (M +1).

Analysis calculated for $C_{10}H_{17}N_3O_2 \cdot HCl$:

C, 48.49; H, 7.32; N, 16.96; Cl, 14.31.

Found: C, 48.71; H, 7.18; N, 17.03; Cl, 14.32.

EXAMPLE 5

[1-(5-Thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-ylmethyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (9)

A mixture of [1-(N-Hydroxycarbamimidoylmethyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (4.85 g, 0.017 mol), 90% 1,1′-thiocarbonyldiimidazole (3.96 g, 0.02 mol) and DBU (10.39 g, 0.068 mol) in MeCN (150 mL) was stirred at room temperature19 hours. The reaction mixture was evaporated to dryness, suspended in saturated KH_2PO_4 and extracted 3X EtOAc. The EtOAc extracts were washed 2X saturated KH_2PO_4, 2X brine and dried over Na_2SO_4. Evaporation followed by filtration through silica gel, eluting with 3:1 EtOAc/hexane yielded, upon evaporation, a solid which was recrystallized from Et_2O/hexane to give a pale pink solid, 2.6 g (47%), mp 160-161°C.

^{1}HNMR ($CDCl_3$) δ 1.1-1.6 (m, 19H), 2.53 (s, 2H), 3.00 (d, 2H, J = 7.33 Hz), 4.90 (t, 1H, J = 7.08 Hz), 12.88 (s, 1H).

MS (APCI) m/z 328 (M + 1).

Analysis calculated for $C_{15}H_{25}N_3O_3S$:

C, 55.02; H, 7.70; N, 12.83; S, 9.79.

Found: C, 55.34; H, 7.80; N, 12.72; S, 9.43.

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazole-5-thione; hydrochloride (10)

[1-(5-Thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-ylmethyl)-cyclohexylmethyl]-carbamic acid tert-butyl ester (9)

(2.5 g, 0.0076 mol) was taken up in 4 M HCl in 1,4-dioxane (75 mL) and stirred at room temperature. The precipitate which formed was filtered off and recrystallized from MeOH- Et_2O to yield 1.31 g (66%) white solid, mp 210-212°C.

^{1}HNMR (DMSO-d_6) δ 1.2-1.5 (m, 10H), 2.79-2.85 (m, 4H), 7.99 (s, 3H).

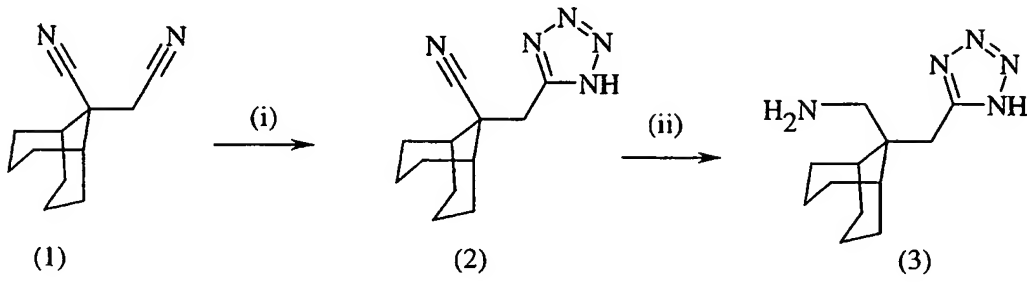
MS (APCI) m/z 228 (M +1).

Analysis calculated for $C_{10}H_{17}N_3OS \cdot HCl$:

C, 45.53; H, 6.88; N, 15.93; S, 12.16; Cl, 13.44.

Found: C, 45.92; H, 6.71; N, 15.83; S, 11.81; Cl, 13.48.

EXAMPLE 6



(1) (2) (3)

Reagents:

(i) Trimethylsilylazide, dibutyl tin oxide, toluene

(ii) Nickel catalyst, Methanol

Synthesis of 9-(1H-Tetrazol-5-ylmethyl)-bicyclo[3.3.1]nonane-9-carbonitrile (2)

To a solution of the bis nitrile (ref WO 9733859) (1.2 g, 6.38 mmol) in toluene (10 mL) was added trimethylsilylazide (1.48 g, 12.87 mmol) followed by dibutyl tin oxide (0.16 g, 0.64 mmol). After heating to 95° for 3 days the mixture was diluted with ethyl acetate, washed with 1N HCl and water, dried over magnesium sulphate, and evaporated to dryness. Crystallization gave the required compound (0.3 g, 20%); mp 189-191°C.

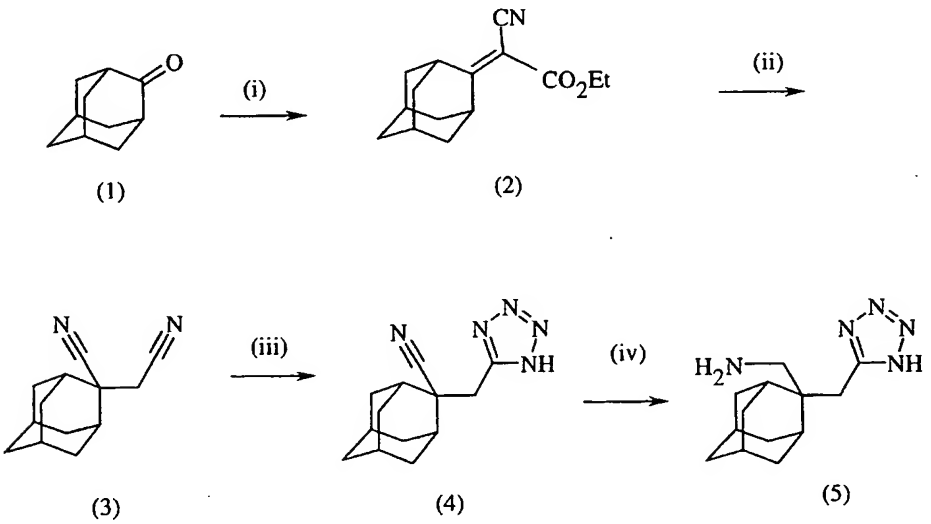
400 MHz NMR (d_6-DMSO) δ 1.50-1.70 (m, 4H), 1.75-2.10 (m, 10H), 3.48 (s, 2H).

Synthesis of C-[9-(1H-Tetrazol-5-ylmethyl)-bicyclo[3.3.1]non-9-yl]-methylamine hydrochloride (3)

The tetrazole obtained in Step 1 (0.60 g, 2.59 mmol) in methanol (100 mL) was added to a washed suspension of nickel catalyst in methanol. The mixture was shaken under 40 psi hydrogen overnight and then filtered to remove the catalyst and evaporated to dryness. The residue was dissolved in methanol and ethereal hydrogen chloride added. Addition of ether and filtration gave the required product (0.19 g, 22%). mp 232-236°C.

400 MHz NMR (d_6-DMSO) δ 1.40–1.70 (m, 8H), 1.75-1.95 (m, 4H), 2.05-2.15 (m, 2H), 3.13 (s, 2H), 3.29 (s, 2H), 8.0 (bs, 3H).

EXAMPLE 7



Reagents:

(i) Ethylcyanoacetate, NaH, THF;

(ii) KCN, EtOH, water, reflux;

(iii) Trimethylsilylazide, dibutyltin oxide, toluene;

(iv) Nickel catalyst, Methanol

Synthesis of 2-(1H-Tetrazol-5-ylmethyl)-adamantane-2-carbonitrile (4)

Prepared in the same manner as 9-(1H-Tetrazol-5-ylmethyl)-bicyclo[3.3.1]nonane-9-carbonitrile in Example 4.

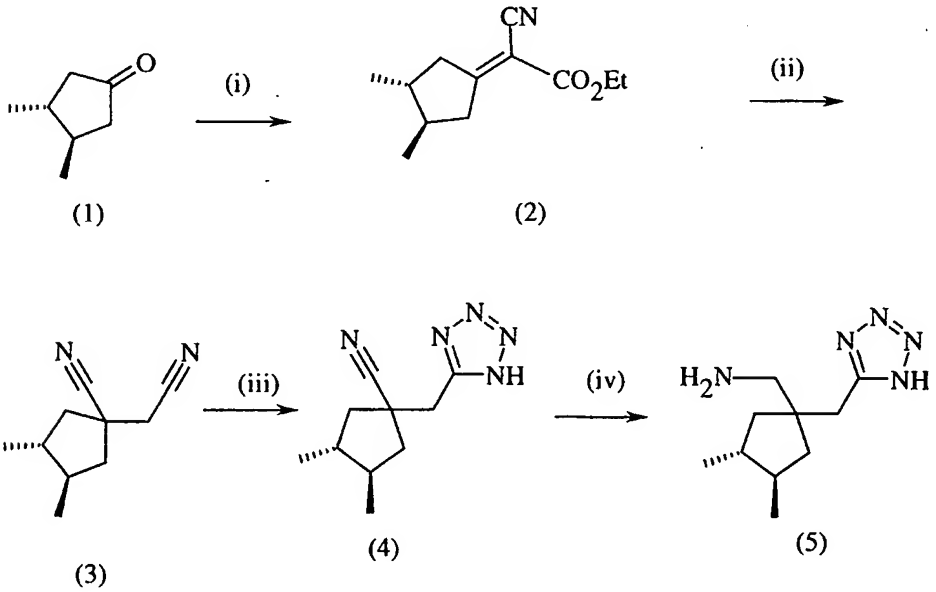
Synthesis of C-[2-(1H-Tetrazol-5-ylmethyl)-adamantan-2-yl]-methylamine hydrochloride (5)

The nitrile obtained in Step 3 was prepared in an analogous manner to (0.47 g, 1.9 mmol) was shaken with nickel catalyst (one spatula full, washed) under 50 psi hydrogen overnight. Filtration through kieselguhr and evaporation followed by treatment with methanol and ethereal hydrogen chloride gave the required product which was crystallized from methanol and acetonitrile (25 mg, 5%); mp 250-252°C.

400 MHz NMR δ 1.49 (s, 2H), 1.54 (d, J = 13.7 Hz, 2H), 1.59 (d, J = 13.7 Hz), 1.67 (s, 2H), 1.83 (s, 1H), 1.90 (s, 1H), 1.97 (d, J = 12.9 Hz, 2H), 2.19 (d, J = 12.7 Hz, 2H), 3.15 (s, 2H), 3.34 (s, obscured by water), 7.99 (bs, 3H).

Mass Spec ES^+ 248 (100%, $(M+H)^+$).

EXAMPLE 8



Reagents:

(i) Ethyl cyanoacetate, ammonium acetate, acetic acid, toluene

(ii) Potassium cyanide, aqueous ethanol

(iii) Trimethylsilylazide, dibutyltin oxide, toluene

(iv) nickel catalyst, methanol

Synthesis of (trans)Cyano-(3,4-dimethyl-cyclopentylidene)-acetic acid ethyl ester (2)

Trans-3,4-dimethyl cyclopentanone (2.91 g, 25.94 mmol), ethyl cyanoacetate (2.93 g, 25.93 mmol), ammonium acetate (0.20 g, 2.60 mmol), and acetic acid (0.31 g, 5.17 mmol) were heated together in refluxing toluene under a Dean-Starck trap for 24 hours. After cooling and filtration through kieselguhr, evaporation gave the required product as an off-white solid (5.0 g, 93%).
400 MHz NMR δ 1.08 (d, J = 6.0 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.55-1.70 (m, 2H), 2.30-2.45 (m, 2H), 3.08 (dd, J = 20.0 Hz, 8.0 Hz, 1H), 3.43 (dd, J = 20.0 Hz, 7.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H).
Mass Spec ES^+ 208.19 $(M+H)^+$, 225.19, 230.16 (100%, $(M+Na)^+$).

Synthesis of (trans)1-Cyanomethyl-3,4-dimethyl-cyclopentanecarbonitrile (3)

The product from Step 1 (5.0 g, 24.1 mmol) was refluxed with potassium cyanide (1.57 g, 24.2 mmol) in ethanol/10%water (50 mL) overnight. Evaporation to dryness and purification by chromatography eluting with ethyl acetate/heptane 1:1 gave the required product as a yellow oil 2.9 g (74%). tlc rf 0.45 ethyl acetate/heptane 1:1.
400 MHz NMR δ 1.05 (d, J = 8.4 Hz, 3H), 1.07 (d, J = 8.8 Hz, 3H), 1.49 (dd, J = 13.2, 11.6 Hz, 1H), 1.60-1.70 (m, 1H), 1.75-1.90 (m, 1H), 1.96 (dd, J = 13.6, 14.8 Hz, 1H), 2.19 (dd, J = 14.0, 8.4 Hz, 1H), 2.48 (dd, J = 13.2, 6.4 Hz, 1H), 2.73 (s, 2H).

Synthesis of (trans)3,4-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentanecarbonitrile (4)

The bis-nitrile from Step 2 (1.62 g, 10 mmol) was heated with trimethylsilyl azide (2.84 g, 24.7 mmol) and di-butyl tin oxide (0.24 g, 0.96 mmol) in toluene (50 mL) to 100°C overnight. The reaction mixture was diluted with ethyl acetate and washed with dilute hydrochloric acid and water. The solution was dried over magnesium sulphate and evaporated to dryness. Purification by chromatography eluting with ethyl acetate gave the required product as a colorless oil 0.94 g, (46%).

Mass Spec ES$^+$ 206.23 $(M+H)^+$, 228.26 $(M+Na)^+$.

400 MHz NMR $CDCl_3$ δ 1.04 (d, J = 7.2 Hz, 3H), 1.05 (d, J = 6.4 Hz), 1.56 (dd, J = 11.6, 11.6 Hz, 1H), 1.55-1.65 (m, 1H), 1.65-1.75 (m, 1H), 1.83 (dd, J = 13.6, 9.2 Hz, 1H), 2.27 (dd, J = 14.0, 8.0 Hz), 2.35 (dd, J = 13.0, 6.8 Hz, 1H), 3.36 (s, 2H).

Synthesis of (trans)C-[3,4-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine hydrochloride (5)

The tetrazole obtained in Step 3 (0.90 g, 0.44 mmol) and nickel catalyst (one spatula full, washed) were shaken together in methanol (200 mL) overnight. The mixture was filtered through kieselguhr and evaporated to dryness. The residue was treated with methanol and ethereal hydrogen chloride and then stirred with di-tertiarybutyl dicarbonate (0.80 g, 3.67 mmol) and sodium bicarbonate (0.80 g, 9.52 mmol) in aqueous dioxan (1:1, 20 mL) overnight. The mixture was diluted with ethyl acetate and the aqueous phase separated, acidified, and extracted 3X with ethyl acetate. The extracts were dried over magnesium sulphate, filtered and evaporated to give a colorless oil. This oil was stirred with 4 M hydrogen chloride in dioxan (5 mL) overnight and then evaporated to dryness to give the required product 0.24 g (76%).

400 MHz d_6-DMSO δ 0.88 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 5.6 Hz, 3H), 1.15-1.25 (m, 3H), 1.35-1.45 (m, 1H), 1.70-1.80 (m, 2H), 2.82 (d, J = 13.2 Hz, 1H), 2.89 (d, J = 13.2 Hz, 1H), 3.04 (d, J = 15.2 Hz, 1H), 3.05 (d, J = 15.2 Hz, 1H).

Mass Spec ES$^+$ 210 100%, $(M+H)^+$.

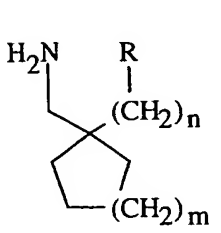
Elemental analysis calculated for $C_{10}H_{19}N_5 \cdot HCl \cdot 0.5H_2O$:

C, 47.14; H, 8.31; N, 27.49.

Found: C, 47.23; H, 7.97; N, 27.16.

CLAIMS

1. The compounds of the invention are those of formula



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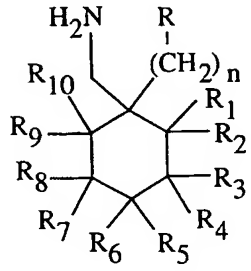

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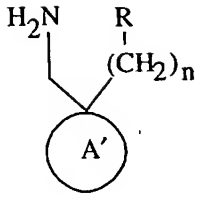

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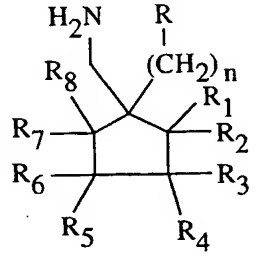

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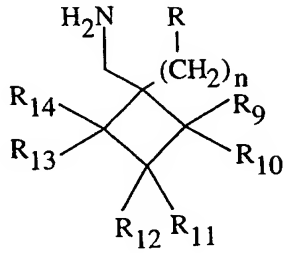


1H

or a pharmaceutically acceptable salt thereof wherein:

n is an integer of from 0 to 2;

m is an integer of from 0 to 3;

R is sulfonamide,

amide,

phosphonic acid,

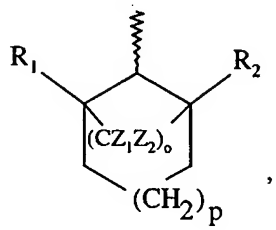
heterocycle,

sulfonic acid, or

hydroxamic acid;

R_1 to R_{14} are each independently selected from hydrogen or straight or branched alkyl of from 1 to 6 carbons, unsubstituted or substituted benzyl or phenyl which substituents are selected from halogen, alkyl, alkoxy, hydroxy, carboxy, carboalkoxy, trifluoromethyl, and nitro;

A′ is a bridged ring selected from



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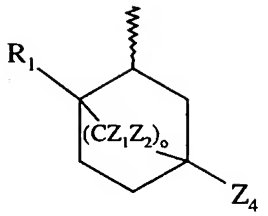
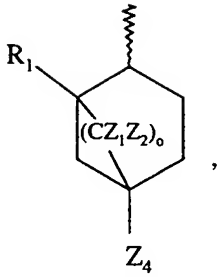
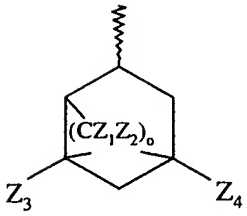


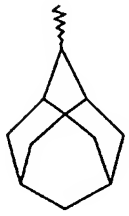
(2)



(3)



, and



(4) (5)

wherein

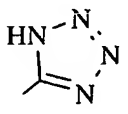
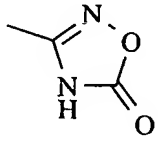
≷ is the point of attachment;

Z_1 to Z_4 are each independently selected from hydrogen and methyl;

o is an integer of from 1 to 4; and

p is an integer of from 0 to 2 with the proviso that in formula 1 R is not $-SO_3H$ when m is 2 and n is 1.

2. A compound according to Claim 1 wherein the formula is 1, m is 2, and

R is  or  .

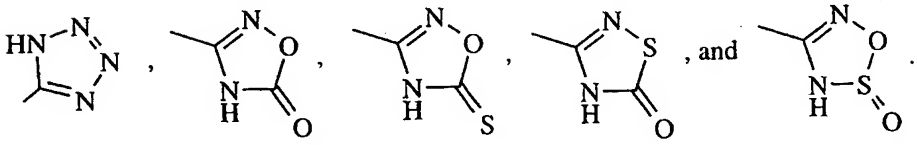
3. A compound according to Claim 1 wherein R is a sulfonamide selected from $-NHSO_2R^{15}$ or $-SO_2NHR^{15}$ wherein R^{15} is straight or branched alkyl or trifluoromethyl.

4. A compound according to Claim 1 named N-[2-(1-aminomethyl-cyclohexyl)-ethyl]-methanesulfonamide.

5. A compound according to Claim 1 wherein R is a phosphonic acid, $-PO_3H_2$.

6. A compound according to Claim 1 and selected from (1-aminomethyl-cyclohexylmethyl)-phosphonic acid and (2-aminomethyl-4-methyl-pentyl)-phosphonic acid.

7. A compound according to Claim 1 wherein R is a heterocycle selected from



8. A compound according to Claim 1 and selected from C-[1-(1H-tetrazol-5-ylmethyl)cyclohexyl]-methylamine, and 4-methyl-2-(1H-tetrazol-5-ylmethyl)-pentylamine.

9. A compound according to Claim 1 and selected from:

(1-Aminomethyl-cyclohexylmethyl)-phosphonic acid;

(1R-trans)(1-Aminomethyl-3-methyl-cyclohexylmethyl)-phosphonic acid;

(trans)(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-phosphonic acid;

(1R-trans)(1-Aminomethyl-3-methyl-cyclopentylmethyl)-phosphonic acid;

(1S-cis)(1-Aminomethyl-3-methyl-cyclopentylmethyl)-phosphonic acid;

(1S-trans)(1-Aminomethyl-3-methyl-cyclopentylmethyl)-phosphonic acid;

(1R-cis)(1-Aminomethyl-3-methyl-cyclopentylmethyl)-phosphonic acid;

(1α,3α,4α)(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-phosphonic acid;

(1α,3β,4β)(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-phosphonic acid;

(R)(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-phosphonic acid;

(S)(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-phosphonic acid;

(1-Aminomethyl-3,3-dimethyl-cyclobutylmethyl)-phosphonic acid;

2-(1-Aminomethyl-cyclohexyl)-N-hydroxy-acetamide;

(1S-trans)2-(1-Aminomethyl-3-methyl-cyclohexyl)-N-hydroxy-acetamide;

(trans)2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

(1S-cis)2-(1-Aminomethyl-3-methyl-cyclopentyl)-N-hydroxy-acetamide;

(1R-trans)2-(1-Aminomethyl-3-methyl-cyclopentyl)-N-hydroxy-acetamide;

(1R-cis)2-(1-Aminomethyl-3-methyl-cyclopentyl)-N-hydroxy-acetamide;

(1S-trans)2-(1-Aminomethyl-3-methyl-cyclopentyl)-N-hydroxy-acetamide;

(1α,3α,4α)2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

(1α,3β,4β)2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

(S)2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

(R)2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-N-hydroxy-acetamide;

2-(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-N-hydroxy-acetamide;

N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclohexyl)-ethyl]-methanesulfonamide;

(trans)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1R-trans)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1R-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1α,3α,4α)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

(1α,3β,4β)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

(S)N-[2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

(R)N-[2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-ethyl]-methanesulfonamide;

N-[2-(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-ethyl]-methanesulfonamide;

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(trans)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1R-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1R-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1S-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1α,3α,4α)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(1α,3β,4β)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(S)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

(R)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(1-Aminomethyl-3,3-dimethyl-cyclobutylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(trans)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1R-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1R-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1S-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1α,3α,4α)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(1α,3β,4β)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(S)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

(R)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

3-(1-Aminomethyl-3,3-dimethyl-cyclobutylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[1-(1H-Tetrazol-5-ylmethyl)-cyclohexyl]-methylamine;

(1S-cis)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclohexyl]-methylamine;

(trans)C-[3,4-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1S-cis)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1R-trans)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1R-cis)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1S-trans)C-[3-Methyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1α,3α,4α)C-[3,4-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(1α,3β,4β)C-[3,4-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(S)C-[3,3-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

(R)C-[3,3-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

C-[3,3-Dimethyl-1-(1H-tetrazol-5-ylmethyl)-cyclobutyl]-methylamine;

N-[2-(1-Aminomethyl-cyclohexyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclohexyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(trans)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1R-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1S-trans)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1S-cis)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1R-trans)N-[2-(1-Aminomethyl-3-methyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1α,3α,4α)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(1α,3β,4β)N-[2-(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(S)N-[2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

(R)N-[2-(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

N-[2-(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

3-(1-Aminomethyl-cyclohexylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclohexylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(trans)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1R-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1S-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1S-cis)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1R-trans)3-(1-Aminomethyl-3-methyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1α,3α,4α)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(1α,3β,4β)3-(1-Aminomethyl-3,4-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(S)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

(R)3-(1-Aminomethyl-3,3-dimethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

3-(1-Aminomethyl-3,3-dimethyl-cyclobutylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[1-(2-Oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclohexyl]-methylamine;

(1S-cis)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclohexyl]-methylamine;

(trans)C-[3,4-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1S-cis)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1R-trans)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1R-cis)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1S-trans)C-[3-Methyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1α,3α,4α)C-[3,4-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1α,3β,4β)C-[3,4-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(S)C-[3,3-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(R)C-[3,3-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

C-[3,3-Dimethyl-1-(2-oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclobutyl]-methylamine;

(1-Aminomethyl-cyclohexyl)-methanesulfonamide;

(1R-trans)(1-Aminomethyl-3-methyl-cyclohexyl)-methanesulfonamide;

(trans)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonamide;

(1S-trans)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonamide;

(1R-cis)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonamide;

(1R-trans)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonamide;

(1S-cis)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonamide;

(1α,3β,4β)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonamide;

(1α,3α,4α)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonamide;

(R)(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-methanesulfonamide;

(S)(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-methanesulfonamide;

(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-methanesulfonamide;

(1-Aminomethyl-cyclohexyl)-methanesulfonic acid;

(1R-trans) (1-Aminomethyl-3-methyl-cyclohexyl)-methanesulfonic acid;

(trans)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonic acid;

(1S-trans)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonic acid;

(1S-cis)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonic acid;

(1R-trans)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonic acid;

(1R-cis)(1-Aminomethyl-3-methyl-cyclopentyl)-methanesulfonic acid;

(1α,3β,4β)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonic acid;

(1α,3α,4α)(1-Aminomethyl-3,4-dimethyl-cyclopentyl)-methanesulfonic acid;

(R)(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-methanesulfonic acid;

(S)(1-Aminomethyl-3,3-dimethyl-cyclopentyl)-methanesulfonic acid;

(1-Aminomethyl-3,3-dimethyl-cyclobutyl)-methanesulfonic acid;

(1-Aminomethyl-cyclopentylmethyl)-phosphonic acid;

2-(1-Aminomethyl-cyclopentyl)-N-hydroxy-acetamide;

N-[2-(1-Aminomethyl-cyclopentyl)-ethyl]-methanesulfonamide;

3-(1-Aminomethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(1-Aminomethyl-cyclopentylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[1-(1H-Tetrazol-5-ylmethyl)-cyclopentyl]-methylamine;

N-[2-(1-Aminomethyl-cyclopentyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

3-(1-Aminomethyl-cyclopentylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[1-(2-Oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cyclopentyl]-methylamine;

(1-Aminomethyl-cyclopentyl)-methanesulfonamide;

(1-Aminomethyl-cyclopentyl)-methanesulfonic acid;

(9-Aminomethyl-bicyclo[3.3.1]non-9-ylmethyl)-phosphonic acid;

2-(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-N-hydroxy-acetamide;

N-[2-(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-ethyl]-methanesulfonamide;

3-(9-Aminomethyl-bicyclo[3.3.1]non-9-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(9-Aminomethyl-bicyclo[3.3.1]non-9-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[9-(1H-Tetrazol-5-ylmethyl)-bicyclo[3.3.1]non-9-yl]-methylamine;

N-[2-(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

3-(9-Aminomethyl-bicyclo[3.3.1]non-9-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[9-(2-Oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-bicyclo[3.3.1]non-9-yl]-methylamine;

(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-methanesulfonamide;

(9-Aminomethyl-bicyclo[3.3.1]non-9-yl)-methanesulfonic acid;

(2-Aminomethyl-adamantan-2-ylmethyl)-phosphonic acid;

2-(2-Aminomethyl-adamantan-2-yl)-N-hydroxy-acetamide;

N-[2-(2-Aminomethyl-adamantan-2-yl)-ethyl]-methanesulfonamide;

3-(2-Aminomethyl-adamantan-2-ylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(2-Aminomethyl-adamantan-2-ylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[2-(1H-Tetrazol-5-ylmethyl)-adamantan-2-yl]-methylamine;

N-[2-(2-Aminomethyl-adamantan-2-yl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

3-(2-Aminomethyl-adamantan-2-ylmethyl)-4H-[1,2,4]thiadiazol-5-one;

C-[2-(2-Oxo-2,3-dihydro-2λ^4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-adamantan-2-yl]-methylamine;

(2-Aminomethyl-adamantan-2-yl)-methanesulfonamide;

(2-Aminomethyl-adamantan-2-yl)-methanesulfonic acid

(1-Aminomethyl-cycloheptylmethyl)-phosphonic acid;

2-(1-Aminomethyl-cycloheptyl)-N-hydroxy-acetamide;

N-[2-(1-Aminomethyl-cycloheptyl)-ethyl]-methanesulfonamide;

3-(1-Aminomethyl-cycloheptylmethyl)-4H-[1,2,4]oxadiazol-5-one;

3-(1-Aminomethyl-cycloheptylmethyl)-4H-[1,2,4]oxadiazole-5-thione;

C-[1-(1H-Tetrazol-5-ylmethyl)-cycloheptyl]-methylamine;

N-[2-(1-Aminomethyl-cycloheptyl)-ethyl]-C,C,C-trifluoro-methanesulfonamide;

C-[1-(2-Oxo-2,3-dihydro-2 l4-[1,2,3,5]oxathiadiazol-4-ylmethyl)-cycloheptyl]-methylamine;

(1-Aminomethyl-cycloheptyl)-methanesulfonamide; and

(1-Aminomethyl-cycloheptyl)-methanesulfonic acid.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

11. A method for treating epilepsy comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

12. A method for treating faintness attacks, hypokinesia, and cranial disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

13. A method for treating neurodegenerative disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

14. A method for treating depression comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

15. A method for treating anxiety comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

16. A method for treating panic comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

17. A method for treating pain comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

18. A method for treating neuropathological disorders comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

19. A method for treating gastrointestinal damage comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

20. A method for treating inflammation comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

21. A method for treating irritable bowel syndrome comprising administering a therapeutically effective amount of a compound according to Claim 1 to a mammal in need of said treatment.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23918

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D257/04 A61K31/41 C07D271/06 C07F9/38 A61K31/66
C07D291/04 C07C311/10 A61K31/18 C07C311/07 C07C239/14
A61K31/16 C07C309/25 A61K31/255

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WALKER G.N. ET AL.: "Synthesis of new 3-(pyridylmethylene)- 3-(pyridylmethyl)-, 3-(piperidylmethyl)-, and 3-(.beta.-alkylaminomethyl)-2-indolinones. The reduction of isoindogenides, nitro compounds, and pyridines in a series of 2-indolinones" JOURNAL OF MEDICINAL CHEMISTRY, vol. 8, no. 9, September 1965, pages 626-637, XP002102295 see formulae Xa, Xb and Xc see page 634 ---	1,10
X	DE 19 10 560 A (N.V. PHILIPS' GLOEILAMPENFABRIEKEN) 9 October 1969 see compound VI see claim 3; example 11A ---	1
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 May 1999	26. 05. 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hartrampf, G

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 22 46 728 A (ALLEN & HANBURYS LTD,) 3 May 1973 see page 37; example 35 see page 46; example 51 ---	1,10
X	HARPER N.J. ET AL.: "1-(3,4-Dichlorobenzamidomethyl)cyclohexyl dimethylamine and related compounds as potential analgesics" JOURNAL OF MEDICINAL CHEMISTRY, vol. 17, no. 11, November 1974, pages 1188-1193, XP002102296 see compound 12 see page 1189 ---	1,10
X	ABDEL RAHMAN M.O. ET AL.: "Synthesis of some 1,1-disubstituted cyclohexanes of potential psychotropic activity" EGYPTIAN JOURNAL OF CHEMISTRY, vol. 18, no. 2, 1975, pages 385-392, XP002102297 see compounds (2) and (9) ---	1,10
X	EP 0 010 401 A (JANSSEN PHARMACEUTICA N.V.) 30 April 1980 see formula II, examples IV, V(5), V(7), V(15), V(17), V(23) and V(25) ---	1
X	DE 33 00 774 A (HOECHST AG) 12 July 1984 see formula XII, example 4b ---	1
X	EP 0 133 318 A (GÖDECKE AKTIENGESELLSCHAFT) 20 February 1985 see claims 1,2,5 ---	1,9,10
X	EP 0 232 813 A (WARNER-LAMBERT COMPANY) 19 August 1987 see example 9 ---	1
X	DE 36 34 066 A (BOEHRINGER MANNHEIM GMBH) 21 April 1988 see example 11 ---	1,10
X	NASSER J. ET AL.: ".alpha.-Functional cycloalkylphosphonates. II. Synthesis of .alpha.-aminomethyl- and .alpha.-(N-substituted)aminomethylcycloalkylphosphonates" PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS, vol. 55, no. 1-4, 1991, pages 137-146, XP002102298 see formula 6, entries 5b, 5c and 5d see page 143; table V ---	1,5,6

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 506 532 A (LIPHA, LYONNAISE INDUSTRIELLE PHARMACEITIQUE) 30 September 1992 see formula 5 see claim 7; examples 1,2,14 ---	1
X	EP 0 557 171 A (LIPHA, LYONNAISE INDUSTRIELLE PHARMACEUTIQUE) 25 August 1993 see formula 5 see claim 5; examples 1,11-14,16 ---	1
X	O'BRIEN P.M. ET AL.: "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 8. Incorporation of amide or amine functionalities into a series of disubstituted ureas and carbamates. Effects on ACAT inhibition in vitro and efficacy in vivo" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 12, 1 January 1994, pages 1810-1822, XP002082610 see compound 23c ---	1
X	SUMAN-CHAUHAN N. ET AL.: "Characterisation of [3H]gabapentin binding to a novel site in rat brain: Homogenate binding studies" EUROPEAN JOURNAL OF PHARMACOLOGY - MOLECULAR PHARMACOLOGY SECTION, vol. 244, no. 3, 15 February 1993, pages 293-301, XP002096653 cited in the application see compounds 6, 7 see page 297; table 1 ---	1,9,10
X	EP 0 625 507 A (NISSHIN FLOUR MILLING CO., LTD.) 23 November 1994 see example 76 ---	1
X	CHEMICAL ABSTRACTS, vol. 123, no. 17, 23 October 1995 Columbus, Ohio, US; abstract no. 227978g, ITO Y. ET AL.: "Urea derivatives as acyl-CoA-cholesterol acyltransferase inhibitors and their preparation" page 1169; column 1; XP002102300 see abstract & JP 07 101929 A (FUJISAWA PHARMACEUTICAL CO.) 18 April 1995 --- -/--	1

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23918

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BOOTH R.J & HODGES J.C.: "Polymer-supported quenching reagents for parallel purification" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 119, no. 21, 1997, pages 4882-4886, XP002102299 see compound 23 see page 4885 ---	1
P,X	WO 98 07718 A (WARNER-LAMBERT COMPANY) 26 February 1998 see formulae II, XXI, XXII, XXIII and XXV see examples 1,26-28,30,31 ---	1
Y	BURGER A.: "Isosterism and bioisosterism in drug design" PROGRESS IN DRUG RESEARCH, vol. 37, 1991, pages 287-371, XP002096229 see page 332 - page 338 ---	1-10
Y	PATANI G.A. & LA VOIE E.J.: "Bioisosterism: A rational approach in drug design" CHEMICAL REVIEWS, vol. 96, no. 8, 1996, pages 3147-3176, XP000652176 see 3. Carboxylate group bioisosteres see page 3168, left-hand column - page 3170, left-hand column ---	1-10
Y	WO 97 33858 A (WARNER-LAMBERT COMPANY) 18 September 1997 see the whole document ---	1-10
Y	WO 97 33859 A (WARNER-LAMBERT COMPANY) 18 September 1997 see the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11-21
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (partially), 3, 4, 9 (partially), 10 (partially)

   Compounds of formulae 1, 1C, 1F, 1G and 1H wherein R is a sulfonamide group and their pharmaceutical compositions containing them

2. Claims: 1, 9, 10 (all partially)

   Compounds of formulae 1, 1C, 1F, 1G and 1H wherein R is an amide group and their pharmaceutical compositions containing them

3. Claims: 1 (partially), 5, 6, 9 (partially), 10 (partially)

   Compounds of formulae 1, 1C, 1F, 1G and 1H wherein R is a phosphonic acid group and their pharmaceutical compositions containing them

4. Claims: 1 (partially), 2, 7, 8, 9 (partially), 10 (partially)

   Compounds of formulae 1, 1C, 1F, 1G and 1H wherein R is a heterocycle moiety and their pharmaceutical compositions containing them

5. Claims: 1, 9, 10 (all partially)

   Compounds of formulae 1, 1C, 1F, 1G and 1H wherein R is a sulfonic acid group and their pharmaceutical compositions containing them

6. Claims: 1, 9, 10 (all partially)

   Compounds of formulae 1, 1C, 1F, 1G and 1H wherein R is a hydroxamic acid group and their pharmaceutical compositions containing them

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 1910560 A	09-10-1969	NL 6804065 A	24-09-1969
		AT 293354 B	15-09-1971
		BE 730206 A	22-09-1969
		ES 364980 A	16-02-1971
		FR 8166 M	24-08-1970
		FR 1604059 A	05-07-1971
DE 2246728 A	03-05-1973	GB 1410011 A	15-10-1975
		AU 475627 B	26-08-1976
		AU 4679872 A	28-03-1974
		BE 789025 A	20-03-1973
		CA 995220 A	17-08-1976
		CH 597153 A	31-03-1978
		FR 2154559 A	11-05-1973
		JP 48039409 A	09-06-1973
		NL 7212967 A	27-03-1973
		ZA 7206282 A	27-06-1975
		US 3975443 A	17-08-1976
		US 4049663 A	20-09-1977
EP 10401 A	30-04-1980	US 4216217 A	05-08-1980
		AT 963 T	15-05-1982
		CA 1128949 A	03-08-1982
		DK 427879 A	14-04-1980
		FI 793181 A	14-04-1980
		JP 55069561 A	26-05-1980
DE 3300774 A	12-07-1984	AT 39931 T	15-01-1989
		AU 575308 B	28-07-1988
		AU 2322984 A	19-07-1984
		DK 11984 A,B,	13-07-1984
		EP 0116276 A	22-08-1984
		GR 79158 A	02-10-1984
		IE 56544 B	28-08-1991
		JP 2042057 C	09-04-1996
		JP 7059590 B	28-06-1995
		JP 59134765 A	02-08-1984
		PT 77943 A,B	01-02-1984
		US 4620012 A	28-10-1986
		ZA 8400213 A	29-08-1984
EP 133318 A	20-02-1985	DE 3327318 C	14-03-1985
		AT 24715 T	15-01-1987
		JP 60051164 A	22-03-1985
		US 4587263 A	06-05-1986
EP 232813 A	19-08-1987	US 4755594 A	05-07-1988
		AU 592728 B	18-01-1990
		AU 6797287 A	06-08-1987
		CA 1270821 A	26-06-1990
		DK 46687 A	01-08-1987
		FI 870371 A	01-08-1987
		JP 62228095 A	06-10-1987
		PH 23342 A	14-07-1989
		PT 84226 A,B	01-02-1988
DE 3634066 A	21-04-1988	DD 270304 A	26-07-1989
		EP 0266558 A	11-05-1988

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/23918

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3634066 A		FI 874388 A	08-04-1988
		JP 63096174 A	27-04-1988
		US 4882342 A	21-11-1989
EP 506532 A	30-09-1992	FR 2674522 A	02-10-1992
		AT 111078 T	15-09-1994
		AU 658609 B	27-04-1995
		AU 1309492 A	01-10-1992
		CA 2063170 A	27-09-1992
		CS 9200895 A	14-10-1992
		DE 69200378 D	13-10-1994
		DE 69200378 T	09-03-1995
		DK 506532 T	20-02-1995
		ES 2064149 T	16-01-1995
		HU 65489 A	28-06-1994
		IE 65366 B	18-10-1995
		IL 101248 A	05-12-1996
		JP 5097802 A	20-04-1993
		KR 9507753 B	14-07-1995
		MX 9201365 A	01-10-1992
		NO 178260 B	13-11-1995
		NZ 242078 A	26-10-1994
		OA 9573 A	31-01-1993
		SI 9210305 A	29-02-1996
		RU 2074179 C	27-02-1997
		US 5219859 A	15-06-1993
		ZA 9202163 A	27-09-1993
EP 557171 A	25-08-1993	FR 2687402 A	20-08-1993
		AT 125257 T	15-08-1995
		AU 658475 B	13-04-1995
		AU 3300593 A	19-08-1993
		CA 2089470 A	15-08-1993
		DE 69300268 D	24-08-1995
		DE 69300268 T	04-04-1996
		DK 557171 T	04-12-1995
		ES 2076827 T	01-11-1995
		GR 3017614 T	31-01-1996
		HR 930180 A	31-10-1995
		JP 6001788 A	11-01-1994
		LT 339 A,B	15-06-1994
		LV 10453 A,B	20-02-1995
		MX 9300745 A	01-09-1993
		NZ 245869 A	26-05-1995
		OA 9775 A	30-11-1993
		SK 9093 A	09-09-1993
		US 5338849 A	16-08-1994
		ZA 9300844 A	08-08-1994
EP 625507 A	23-11-1994	CA 2123728 A	22-11-1994
		DE 69404382 D	04-09-1997
		DE 69404382 T	05-03-1998
		JP 7258200 A	09-10-1995
		US 5621010 A	15-04-1997
WO 9807718 A	26-02-1998	AU 4146697 A	06-03-1998
WO 9733858 A	18-09-1997	AU 2051197 A	01-10-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/23918

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9733858 A		CA 2244912 A	18-09-1997
		CZ 9802863 A	17-03-1999
		EP 0888286 A	07-01-1999
		NO 984205 A	14-09-1998
		PL 328816 A	15-02-1999
WO 9733859 A	18-09-1997	AU 2127197 A	01-10-1997
		CA 2245647 A	18-09-1997
		CZ 9802875 A	17-02-1999
		EP 0888285 A	07-01-1999
		NO 984204 A	11-09-1998
		PL 328800 A	15-02-1999